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SUPPLEMENTUM 145

A K K K LUNDSGAARD EDI COEPTA

The Influence of Antifibrinolytica on Traumatic Hyphaema and Corneal Oedema

by

Thorkild Bramsen

SCRIPTOR COPENHAGEN 1980

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Contents

This monograph is based on the following publications

I *Bramsen T* (1976) Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid *Acta ophthal (Kbh) 54* 250 256

II *Bramsen T* (1977) Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid II *Acta ophthal (Kbh) 55* 616 620

III *Bramsen T* (1979) Fibrinolysis and traumatic hyphaema *Acta ophthal (Kbh) 57* 447 454

IV *Bramsen T & Ehlers N* (1977) Bullous keratopathy (Fuchs endothelial dystrophy) *treated systemically with 4 trans amino cyclohexano* carboxylic acid *Acta ophthal (Kbh) 55* 665 673

V *Bramsen T Corydon L & Ehlers N* (1978) A double blind study of the influence af tranexamic acid on the central corneal thickness after cataract extraction *Acta ophthal (Kbh) 56* 121 126

VI *Bramsen T* (1978) A double blind study on the influence af tranexamic acid on the intraocular pressure and the central corneal thickness after trabeculectomy for glaucoma simplex *Acta ophthal (Kbh) 56* 998 1005

VII *Bramsen T* (1979) Serum and aqueous humour concentration of tranexamic acid after peroral administration *Acta ophthal (Kbh) 57* 455 460

VIII *Bramsen T* (1978) The effect of urokinase on central corneal thickness and vitreous haemorrhage *Acta ophthal (Kbh) 56* 1006 1012

IX *Bramsen T & Ehlers N* (1979) Early postoperative changes in graft thickness after penetrating keratoplasty *Acta ophthal (Kbh) 57* 258 268

Introduction

Astrup (1978) writes It is perhaps not usually realized how extensive the impact of fibrinolysis on the living organism is Fibrinolysis is one of the broadest of the fundamental processes of physiology Plasminogen being a precursor of humoral origin is ubiquitously available for activation in the organism Cell death causing the release of thromboplastic compounds and of activators of plasminogen occurs daily in all of us either as a result of the normal turnover of cells during growth maturity and senescense or by tissue damage This means that fibrinolysis is involved in most pathological processes in the body

In connection with pathological conditions in the eye especially haemorrhages has regulation af the fibrinolytic system been used in treatment Oeri (1952) assumed that fibrinolytic activity in the aqueous humor was responsible for the dissolution of the blood clot i traumatic hyphaema In investigations on the contents af various fibrinolytic factors in primary and second aqueous humor from humans and animals it was shown that the aqueous humor contained these factors and in some investigations the contents in the secondary aqueous humor were highest (Deutsch & Zwiauer 1952 Franceschetti & Eichenberger 1959 Pandolfi et al 1964 Pandolfi 1969) In order to activate the dissolution of the blood clot fibrinolysis was experimentally activated in the anterior chamber by parenteral administration of streptokinase trypsin and other fibrinolysis activating drugs (Hopen & Campagna 1955 Keeney & Zaki 1957 Schenk & Trichtel 1957 Liegl 1958 Hoffman 1959 Binder et al 1961 Pandolfi et al 1966) Direct injection into the anterior chamber of fibrinolysis activating enzymes has also been attempted in humans and animals (Jukofski 1951 Friedman 1953 Horven & Opsahl 1964 Berger 1962 Sinskey & Krichesky 1962 Morten & Turnbull 1964) The results af these treatments vary and there is considerable disagreement as to their efficiency

Concerning corpus vitreous haemorrhages an activation of the fibrinolytic system has been attempted (Chandler & Rosenthal 1958 Schimek & Steffensen 1955 Williamson & Forrester 1973 Chapman Smith & Crock 1977) Pandolfi (1969) finds a lack in plaminogen activators in the corpus vitreous which explains why an activating treatment seems reasonable In agreement with this

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An inhibition of the fibrinolytic system in pathological conditions has been succesfully attempted in central serous chorioretinopathy (Yasuyuki 1976) in malignant choroidal melanomas (Bramsen 1978) and in preventing secondary haemorrhages after traumatic hyphaema in four patients (Watkins & Venable 1974)

In investigations concerning fibrinolytic activity in various ocular tissues a high fibrinolytic activity has been found in the endothelial cells of the central *retinal artery (Pandolfi 1967) from the vessels of the corpus ciliaris and iris* (Pandolfi & Kwaan 1967) from the corneal epithelium and endothelium especially from traumatised cells (Pandolfi & Astrup 1967) The fibrinolytic activity in the cornea could be inhibited by tranexamic acid (Pandolfi et al 1972)

The purpose of the present investigation has been to analyse whether an antifibrinolytic treatment can influence some conditions which might arise on a fibrinolytic basis (secondary haemorrhages in traumatic hyphaema) and to what extent this treatment influences the ocular structures known to contain fibrinolytic activity (the cornea)

CHAPTER I

The fibrinolytic system

Fibrinolysis means the proteolytic dissolution of fibrin by means of plasmin (fig. 1)

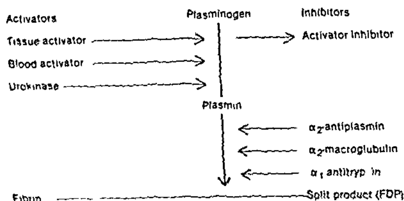


Fig. 1

This process leads to the formation of high molecular fibrin degradation products (FDP); the concentration of this in the blood can serve as a parameter in the [illegible] of the fibrinolytic status of the patients (Patrick 19[illegible]7). Plasmin is a [illegible] protein[illegible] which is capable of dissolving many proteins (e.g. casein) in a [illegible] system. Under physiological circumstances plasmin almost exclusively [illegible] fibrin [illegible] plasmin is specifically attached to fibrin.

Bl[illegible] contains a proenzyme (plasminogen) which, when activated, changes in[illegible] the [illegible] enzyme plasmin. This reformation in the organism takes place by means of [illegible] which are present or formed in many tissues and body fluids.

In the organism, the effect of plasmin and plasminogenic activators is regulated by inhibitors present in the blood and extravascular body fluids. Fibrinolysis is a complex mechanism subjected to constant intensive [illegible]tigation.

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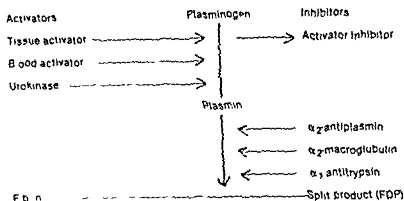
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forming plasminogen into plasmin (Christens n 1945 Mullertz & I assen 1953 Gonzales Gronow et al 1978)

Activa ors are present in a number of tissues (Tissue activators) in blood (B ood activators) and in the extravascular body fluids including urine (Urochinasis)

Tissue activators

The w rk on ti sue activators started when it was shown that cell cultures in vivo were sometimes capable of di solving a coagulum The presence of activators in tissues and tis ue cultures was first established in 1947 (Astrup & Permin) and since then intensive studies on th se activators and their localisation have been carried out (for a survey see Astrup 1978) When Todd (1959) introduced a first chemical technique in which the dissolution of a fibrine film over a tissue secti n showed the localisation of enzymes on the cellular level and Albrechtsen (1959) d scribed a methode of extraction thus making it possible to quantitate the activisation in tissue it was made feasible to carry out investigations on fibrinolytic activity in various tissues Todd (1964) found that endothelium cells in veins were rich in tis ue activators and after trauma the normally inactive arterial endothelium was found to be fibrinolytically active Landolti & Astrup (1957) found a varying fibrinolytic activity localised in the corneal epithelium Inci sions form intact corneas often showed a lack of fibrinolytic activity while epithelium cells mechanically removed from the corneas were fibrinolytically a tive In the same in estigation a high fibrin ly tic activity was found localised in the c rneal endothelium in particular it was established that degeneratively transfo rmed cells or cells exposed to trauma were especially fibrinolytically acti e

Wushmann Henderson & Astrup (1974) investigated the fibrinolytic activity in embry nic rat s tongue and found that the epithelium of the tongue at the m ment f extra tion sh wed no fibrinolytic activity During a cultivation of six days th amount of plasminogen acti ators in the epithelium cells rose several hundred times and at the same time the cultivation medium became fibrin lyti ally a tive Astrup (1978) mentions the possibility that the varying fibrin lysis in different tissues and i cells may reflect a varying content of tissue inhibit rs The hemical characteristics of the tissue activators are incompletely xplained The m lecular weight is ab ut 60 000 (Kok & Astrup 1969)

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The high fibrin lytic activity in blood extracted post mortem has long been kn wn The exi tence f bl od activat rs was evidenced by Mullertz (1953) High a ti ity in bl od i rea he l after physical exertion and mental stress (Biggs

Plasminogen – plasmin

Plasminogen is found in the intravascular space and the concentration in human plasma is approximately 2.4 μmol/l. Plasminogen consists of a single peptide chain with a molecular weight of some 90 000 (Summaria et al. 1972, Wallen 1976). The half life of plasminogen is in vivo around 2.2 days, most of it is metabolised and only an insignificant amount under normal circumstances is transformed into plasmin (Collen et al. 1972, Zolten et al. 1972).

When plasminogen is activated into the active enzyme plasmin, an activator catalysed cleavage of an arginyl valyl binding in the COOH terminal end of the plasminogen molecule takes place. In this way it is divided into a heavy (M = 65 000) and a light (M = 25 000) peptide chain, which is bonded by two disulfide bindings (Robbins et al. 1967). The light chain is responsible for the decomposition of fibrin, the heavy one contains the binding site of fibrin (Robbins et al. 1967, Robbins et al. 1973). During the activisation of plasminogen a few seried peptide bindings in the N terminal part of the plasminogenetic molecule or a corresponding area of the N terminal part of the heavy plasmin chain may also be split. This leads to a cleavage of peptide fragments (total M = 8 000). This proces may be catalyses by plasmin and lead to the uncovering af fibrin binding sites on the plasminogenetic (plasmin) molecule. The result of this is that the arginyl valyl bindings in plasminogen become more easily accesible to an activator.

The formation and decomposition of fibrin

Fibrinogen with a molecular weight of about 340 000 (Caspary & Kekwick 1957) is found in the plasma in a concentration of 8.8 μM/l. Under the influence of thrombin, fibrinogen is transformed into activated fibrinogen, which aggregate and precipitate as fibrin (Doolittle 1973).

Plasmin is capable of decomposing this fibrin thus forming various fragments in the blood. These are known as fibrin degradation products (FDP) (Patrick 1977).

Activators of the fibrinolytic system

Plasminogen activators are found widely distributed in the organism. They play a fundamental role in the restoration of tissue injuries by inducing the resorption of intravascular end extravascular fibrin in the injured area (Astrup & Thorsen 1972). Streptokinase, produced by *streptococci*, *was the first known activator* which was isolated and studied in its pure form. Together with a combination with plasminogen streptokinase forms an active complex capable of trans-

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Activators are present in a number of tissues (Tissue activators), in blood (Blood activators) and in the extravascular body fluids, including urine (Urokinase).

Tissue activators

The work on tissue activators started when it was shown that cell cultures in vivo were sometimes capable of dissolving a coagulum. The presence of activators in tissues and tissue cultures was first established in 1947 (Astrup & Permin), and since then, intensive studies on these activators and their localisation have been carried out (for a survey, see Astrup 1978). When Todd (1959) introduced a histochemical technique, in which the dissolution of a fibrine film over a tissue section showed the localisation of enzymes on the cellular level, and Albrechtsen (1[illegible]) described a methode of extraction thus making it possible to quantitate the activation in tissue, it was made feasible to carry out investigations on fibrinolytic activity in various tissues. Todd (1964) found that endothelium cells in veins were rich in tissue activators, and after trauma, the normally inactive arterial endothelium was found to be fibrinolytically active. Pandolfi & Astrup (196[illegible]) found a varying fibrinolytic activity localised in the corneal epithelium. Incisions from intact corneas often showed a lack of fibrinolytic activity, while epithelium cells mechanically removed from the corneas were fibrinolytically active. In the same investigation, a high fibrinolytic activity was found localised in the corneal endothelium; in particular, it was established that degeneratively transformed cells or cells exposed to trauma were especially fibrinolytically active.

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B[illegible] activators

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et al 1947) After venous stasis and after a stimulation by various vasoactive drugs an increased activity is likewise found (Genton et al 1961) It is not yet established whether the activators formed by the various stimulations are identical (Astrup 1978)

It is most likely that blood activators originate from the vascular endothelium (Nielsson & Pandolfi 1970) but definite information about the place of formation is not yet available In some investigations (Iatridis & Ferguson 1962 Kamplan & Austen 1973) activated Hageman factor seems to be influential in the formation of blood activators but whether this activating machanism is also important in vivo remains yet to be proved

Urokinase

Urokinase is a colourless crystalline substance with a molecular weight of about 50 000 Urokinase is probably different from blood activators (Williams 1951) Urokinases also differs from tissue activators Among other things urokinases is bound to fibrin to a far less extent than the tissue activators (Thorsen et al 1972)

Urokinases is probably formed by the epithelium in the urinary system and the urine is rich in this activator substance Very high concentrations of inhibitors are found in blood which thus modify fibrinolytic activity In urine the inhibition is weak (Egeblad & Astrup 1966)

The regulation of the fibrinolytic activity in urine in spite of the weak inhibition must be explained by the low affinity between fibrin and urokinases This results in the necessity of using high concentrations of urokinases when this substance is clinically used for the dissolution of a blood coagulum

Inhibitors of the fibrinolytic system

It is regarded as likely that the fibrinolytic system can be inhibited in two different places Firstly the activation of plasminogen may be inhibited secondly the influence of plasmin on fibrin may also be inhibited (fig 1)

Activator inhibitor (The labile inhibitor)

The term activator inhibitor which is widely used is misleading insofar as the effect mechanism of this inhibitor is unknown It is a potent labile inhibitor of activator induced fibrinolysis and it is formed during the coagulation of blood (Helle 1968 Bennet 1970 Thorsen 1973 Hedner 1973 Hedner & Collen 1976) The inhibitor has not yet been physically identified The content is investigated by the method described by Parakevas et al 1962 The labile

inhibitor represents a substantial part of the inhibitor capacity. It is still uncertain whether the labile inhibitor consists of several different inhibitors, but clarification of the question is of the greatest importance, as an inhibition at an early stage of fibrinolysis might have a considerable physiological impact (Astrup 1978).

α₂ antiplasmin and α₂ macroglobin

α_2 antiplasmin and α_2 macroglobulin are regarded as being the most important inhibitors of plasmin. Both these inhibitors are potent and they inactivate plasmin rapidly and irreversibly. α antiplasmin was only recently discovered (Mullertz 1974, Mullertz & Clemmensen 1976, Collen et al. 1975, Moroi & Aoki 1976). The molecular weight is 65 000 and this inhibitor reacts with plasmin before α_2 macroglobulin. In the reaction with plasmine 1:1 molar complexes are formed and the inhibitor shows marked specificity. α_2 macroglobulin with a molecular weight of 725 000 is found in plasma at × 1.5 larger molar concentration than plasminogen, and by the inactivating a molecule of α macroglobulin forms a complex with a plasmin molecule (Barret & Starkey 1973).

α antitrypsin

This inhibitor can inactivate plasmin in vitro systems (Herca 1974). During recent years doubt has been raised about the importance of the inhibitor in vivo (Mullertz 1974, Collen et al. 1975). Together with antichymotrypsin, fibrinogen, haptoglobin and orosomucoid, α_1 antitrypsin belong to the socalled C reactive proteins. These proteins react by an increase in serum concentration following surgical intervention, and in connection with inflammatory conditions. The concentration reaches its highest level after about a week, after which a decrease [illegible] (Johansson 1976). The importance of this reaction is unknown. Teger Nilsson et al. (1977) showed that α antiplasmin also increases after surgical intervention and that this inhibitor may belong to the same group of C reactive protein.

[illegible] inhibitors

In [illegible] species of animals and plants a large number of polyvalent proteinase inhibitors have been found with molecular weights of between 5 000 and 10 000 (for a survey see Thorsen 1977). Some of these are potent [illegible] inhibitors. In man a weak plasmin inhibitor is known to exist in [illegible] (Kwaan & Astrup 1965). An inhibitor of activator induced fibrinolysis has been isolated from the placenta (Aoki & Kawano 1972). Noordhoed Heel & Blokmen (1974) found an inhibitor of fibrinolysis in the walls of human arteries. The importance of these tissue inhibitors is still uncertain.

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CHAPTER II

Traumatic hyphaema
(articles I II and III)

Traumatic hyphaema occurs when trauma to the eye is extensive enough to cause a haemorrhage in the anterior chamber The size of these primary haemorrhage is dependent upon the size of the damaged iris vessel the laceration of this and the ability of the individual patient to stem the primary haemorrhages In connection with the trauma various other lesions may occur varying from rupture of the bulbus to discreet changes in the form and size of the pupil These investigation on traumatic hyphaema deals with haemorrhages in the anterior chamber which are macroscopically visible but without any perforating lesions

In an investigation of 360 patients with traumatic hyphaema Beale & Wood (1973) found that at the time of the postexamination (on a average 7 9 months after the trauma) 70% had a visual acuity of between 20/20 and 20/50 6% had a visual acuity of 20/20 or less The same investigation found a secondary haemorrhage frequency of 10% The latter always occurred while the patient were hospitalised and in 69% of the cases from the 3rd to the 6th day after the trauma No difference in secondary haemorrhage frequency was found in patients with and without iris dialysis

As a result of the trauma injuries may occur to the eye which are responsible for reduced visual acuity (cataract choriodal rupture etc) and naturally treatment must also be aimed at these problems One serious complication however is that of secondary haemorrhages which in most cases are more extensive than the primary ones

These secondary haemorrhages cause serious injuries to the ocular structures (e g secondary glaucoma haemocheromatosis) (Raskusin 1972) The frequency of secondary haemorrhage is quoted differently in the literature

With conservative treatment Morris (1960) reported a secondary haemorrhage frequency of 17% Gregersen (196?) using the same treatment reported 5 6% Ohrstrom (1972) found a secondary haemorrhage frequency of 2 4% when the patient was treated with bed rest and topical atropine and steroid Bengtsson & Flinger (1975) reported a secondary haemorrhage

The influence of tranexamic acid on the fibrinolytic system

Thorsen (1978) showed that tranexamic acid forms reversible complexes with both plaminogen and plasmin thereby preventing the binding of these substances to fibrin. The results of this is that the activators cannot transform plasminogen into plasmin. As plasmin cannot be bound to fibrin in the presence of tranexamin acid, it is easier for the naturally occurring inhibitors to neutralise the plasmin. Thus tranexamic acid exerts an inhibitory influence on the transformation of plasminogen into plasmin, at the same time as it increases the plasmin neutralising effect and the naturally occurring inhibitors.

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With conservative treatment, Morris (1960) reported a secondary haemorrhage frequency of 1[illegible]%, Gregersen (1962) using the same treatment reported 5.6%. Ohrstrom (197[illegible]) found a secondary haemorrhage frequency of 2.4% when the patient was treated with bed rest and topical atropine and steroid. Bengtsson & Ehinger (1975) reported a secondary haemorrhage

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frequency of 5.3% using conservative treatment. A secondary haemorrhage frequency of about 6% must be expected with conservative treatment in the Scandinavian countries.

The primary haemorrhage is stopped by the aggregation of thrombocytes in the vessel laceration, the vessel constricts and fibrin is precipitated. As a result of the trauma, tissue activators are liberated, which can transform plasminogen into plasmin and so start fibrinolysis which leads to dissolution of the primarily formed coagulum. Fibrinolytic haemorrhages usually occur a few days after the trauma. The time when secondary haemorrhages occur (The 3rd to 5th day after the trauma) is consequently consistent with a fibrinolytic genesis. Pandolfi (1978) reports that the chamber fluid in patients with secondary haemorrhages may contain a high concentration of FDP, which supports the theory of a fibrinolytic genesis.

Personal investigations

Materials and methods

The investigation was performed on 449 patients with traumatic hyphaema. The patients all had a macroscopically visible hyphaema without penetrating ocular lesions. 135 of the patients were hospitalised in the period from 1965 to 1968 and were treated with bed rest and stenopaeic spectacles. These patients were given no form of medical treatment.

The remaining 310 patients were referred to the department in the period from 1.1.75 to 1.10.78 and were treated with tranexamic acid 25 mg/kg bodyweight three times daily for six days. In the period from 1.1.75 to 31.12.75 the patients (72 patients) received bed rest and stenopaeic spectacles for five days apart from antifibrinolytic treatment and were then discharged with tranexamic acid for a further 24 hours. In the period from 1.1.76 to 31.12.77 (75 + 78 patients) the patients were confined to the department but out of bed and were given, as their only treatment, tranexamic acid in the above mentioned dosis and duration. In the period from 1.1.78 to 1.10.78 (85 patients) the patients was discharged after examination at the department and encouraged to continue their usual work. These patients were treated with tranexamic acid as described.

Four patients with traumatic hyphaema occurring in the summer of 1978 were hospitalised for 7 days and treated conservatively with bed rest and stenopaeic spectacles. In these patients daily measurement of central thickness were taken together with blood samples to determine the serum content of activator inhibitor.

The age and sex distribution of the 310 patients treated with tranexamic acid

and the 135 conservatively treated patients in the period from 1965 to 1968 are illustrated i table I

No patients	Tranexamic acid treated	Control series (1965-68)
Females	60	31
Males	250	104
Average age Females (years)	21 6	15 6
Average age Males (years)	21 6	21 5

T ble I

At the time of confinement the patients were subjected to slit lamp exami nation ophthalmoscopy measurement of intraocular tension and determination of visual acuity Intraocular tensions of more than 30 mm Hg were treated with acetazolamide Table II illustrates the ocular lesions occuring together with the traumatic hyphaema in the 310 patients trated with tranexamic acid

Other eye lesions in the 310 patients with traumati hyphaema treated with tranexamic acid

	No
Subconjunctival haemorrhage	37
Corneal erosion	80
Pupillary changes	155
Iridodialysis	12
Increased intraocular tension at hospitalization	23
Traumatic cataract	10
Retinal haemorrhage	19
Central retinal oedema	30
Choroidal rupture	9
No asociated lesions	43
No of patients	310

T bl II

All the patient treated with tranexamic acid were followed up examined at the department 12 days after the trauma In patients of more then 10 years age gonioscopy was carried out to determine whether synecchiae had occured at the site of the clot

Four male patients were studied for daily determination of the activator inhibitor content of the serum and for daily measurement of the thickness of central cornea (ages 22 23 24 and 54) Other lesions than hyphaema are indicated in Table III The thickness of central cornea was measured as described by Ehlers & Sperling (1977) Activator inhibitor was determined by the method proscribed by Paraskevas et al (1962)

Other eye lesions in 4 patients with traumatic hyphaema who did not receive the antifibrinolytic treatment	No
Subconjunctival haemorrhage	1
Corneal erosion	2
Pupillary changes	3
Increased intraocular tension	1
No	4

Table III

Results

Among the 310 patients treated with tranexamic acid one secondary haemorrhage occured This secondary haemorrhage occured in the group from 1975 who were apart from tranexamic acid treated with bed rest and stenopaeic spectacles The patient was not hospitalised until 36 hours after the initial trauma and the secondary haemorrhage occured 58 hours following the trauma The secondary haemorrhage was modest and the antifibrinolytic treatment was continued No lasting injuries occured to the eye and on the twelfth day the visual acuity was 1 0 Among those ambulatory patients and those treated as out patients no secondary haemorrhages occured The vast majority of the out patients continued there normal work So in this material there is a secondary haemorrhage frequency of 0 32%

The follow up examination on the twelfth day of the patients treated with tranexamic acid showed visual acuities as illustrated in Table IV 12 patients did not appear for the follow up examination

The visual acuity of the follow up examination on the 12th day of 298 patients with traumatic hyphaema treated with tranexamic acid Visual acuity	No
≥1 0	221
0 5 0 9	49
0 3 0 4	13
0 1 0 2	13
≤0 1	2

Table IV

Gonioscopy in 239 patients with traumatic hyphaema treated with traumatic acid. The investigation was performed with regard to goniosynechiae

No	No goniosynechiae	Goniosynechiae
239	222	17

Table V

Among the 133 patients from the period of 1965 to 1968 who were treated with bed rest and stenopaeic spectacles but did not receive any antifibrinolytic treatment there were 9 secondary haemorrhages corresponding to a secondary haemorrhage frequency of 6.7%. This frequency is in accordance with former surveys from Denmark (Gregersen 1962).

Among the four patients confined to bed for measurement of central corneal thickness and for determination of activator inhibitor no secondary haemorrhages occured. Fig 2 (page 18) shows the changes in the thickness of central cornea and the fluctuations in the serum content of activator inhibitor (x ± sem).

It can be seen that the thickness of central cornea increased after the trauma. The oedema remained unchanged for the first two days to be followed by a decrease in the thickness on the 6th day and then once again a decrease occurs. The activator inhibitor content in the serum shows a tendency of a decrease during the first two days. After this an increased content in the serum is produced which reaches its highest level on the 5th day. In the period during which the content of activator inhibitor in the serum increases the thickness of central cornea decreases. The fifth to the sixth day after the trauma produces a drastic decrease in the content of activator inhibitor and a simultaneous secondary increase in the thickness of the central cornea.

Discussion

For many years antifibrinolytic treatment of recurrent haemorrhages has been used for the treatment of other recurrent haemorrhages. In connection Epistaxis Petruson (1974) showed in a double blind investigation that tranexamic acid significantly reduced the frequency of secondary haemorrhage. Watkins & Venables (1974) used the antifibrinolytic drug - ε aminocaproic acid for the treatment of recurring hyphaema in four patients with a good effect. Crough & Frenkel (1976) investigated the influence of the same drug on the frequency of secondary haemorrhages in conection with traumatic hyphaema and in a double blind investigation found a convincing effect of antifibrinolytic drugs.

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Jerndal & Frisen (1976) carried out a double blind investigation on

haemorrhages after cataract operations and found that these were significantly reduced in the group with tranexamic acid

An antifibrinolytic treatment is prophylactic Examples exist in the literature of treatment of hyphaema with urokinase which activates fibrinolysis Most investigations have been carried out on animals (rabbits) and the results can be transferred to humans As already mentioned the results of these investigations vary and urokinase is now only used if the anterior chamber is completely filled with blood

This investigation shows that antifibrinolytic treatment with tranexamic acid can reduce the frequency of secondary haemorrhages after traumatic hyphaema and that the treatment is so effective that bed rest and confinement in hospital are unnecessary Fibrinolysis is known to increase under physical exertion (Biggset et al 1947) so conservative treatment using bed rest is rational but is superflous when antifibrinolytic drugs are used

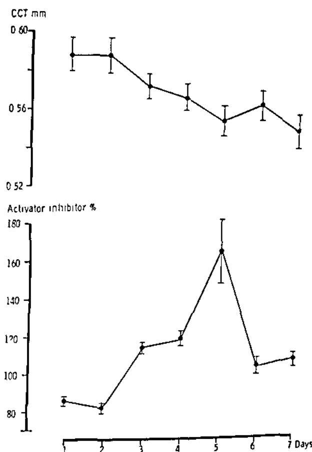


Fig 2

The average curve of the variations in the serum content of activator inhibitor and the average curve of the variations in the central corneal thickness (x ± sem) in *four patients* with traumatic hyphaema

The principle of treatment presupposed that secondary haemorrhages occur on fibrinolytic basis The time at which they occur and the good results with antifibrinolytic drugs speak in favour of such a genesis It would be desirable to have daily measurements of the fibrinolytic activity in the chamber fluid in humans with traumatic hyphaema but for ethical and practical reasons this is not possible Instead of investigating the aqueous the serum content of activator inhibitor has been followed with daily blood samples The content in the serum of this factor is known to change after surgical intervention

Ygge (1972)found an increased content of this factor during the first 5 to 6 days after surgical intervention in the abdomen This increase was substituted by a strong decrease around the 7th day Other investigations have shown corresponding changes Rammer & Saldeen 1970 Knight et al 1977 showed that the changes in fibrinolytic activity after traumas were independent of the size of the operation trauma but dependent on individual differences Investigations showed that 81% reacted with a decrease in fibrinolytic activity in the days after the trauma while 19% had an increased fibrinolytic activity in the serum after a trauma and the decrease was slow and weak The possibility exists that it is among these 19% that the secondary haemorrhages occur In the four investigated patients an increase in the content of inhibitor was found in the serum during the days after the trauma and these patients must be supposed to have a low fibrinolytic activity during that time and indeed no secondary haemorrhages occured The investigation shows a connection between the fluctuations of activator inhibitor and the variation in the thickness of central cornea after the trauma The thickness of cornea is reduced when the content of activator inhibitor is increased in the serum and when the marked decrease in the inhibitor content occurs between the 5th and the 6th day after the trauma this is followed by an increase in the thickness of the cornea It is not possible to know beforehand which patients will be able to inhibit fibrinolysis sufficiently and bearing in mind the serious consequences of secondary haemorrhages all patients should be treated with antifibrinolytic drugs

Mortensen & Sjolin (1978) investigated the effect of tranexamic acid on traumatic hyphaema 64 patients were treated as out patients with tranexamic acid The doses the duration of the treatment and the follow up examinations were entirely identical to those of the present investigation No secondary haemorrhages occurred In a monitoring material consisting of 56 patients confined to bed at the department and not treated antifibrinolytically 3 secondary haemorrhages occurred (5 35%) The material is too small for statistical treatment but in that investigation antifibrinolytic treatment was 100% effective

It must be attempted to prevent any increase in fibrinolytic activity in the

haemorrhages after cataract operations and found that these were significantly reduced in the group with tranexamic acid

An antifibrinolytic treatment is prophylactic. Examples exist in the literature of treatment of hyphaema with urokinase which activates fibrinolysis. Most investigations have been carried out on animals (rabbits) and the results can be transferred to humans. As already mentioned the results of these investigations vary and urokinase is now only used if the anterior chamber is completely filled with blood

This investigation shows that antifibrinolytic treatment with tranexamic acid can reduce the frequency of secondary haemorrhages after traumatic hyphaema and that the treatment is so effective that bed rest and confinement in hospital are unnecessary. Fibrinolysis is known to increase under physical exertion (Biggs et al 1947) so conservative treatment using bed rest is rational but is superfluous when antifibrinolytic drugs are used

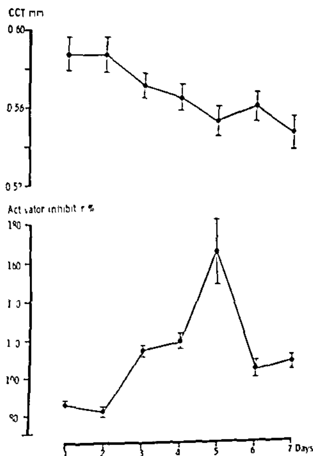


Fig 2

The average curve of the variations in the serum content of activator inhibitor and the average curve of the variations in the central corneal thickness (x ± sem) in four patients with traumatic hyphaema

CHAPTER III

Corneal oedema

The transperancy of the cornea is crucial for normal visual function. Corneal oedema reduces transparency and so it is important to maintain a constant normal thickness of the cornea. In newborn humans the thickness of the cornea is above average and the cornea does not reach a stable thickness until the age of three years (Ehlers et al. 1976). Henceforth the thickness of central cornea remains constant throughout life (von Bahr 1948, Lavergu & Kelecom 1962, Martola & Baum 1968, Kruse Hansen 1971). The regulation mechanism behind this constant thickness of the cornea still remains obscure in spite of intensive research. This may seem paradoxical as the cornea is an easily visible organ, but for ethical reasons human examinations in vivo have been limited. Most attempts to clarify the regulating mechanism have therefore been made on animals, especially rabbits, and it is unknown whether there exist different regulating mechanisms in different species. Many examinations have been made of human post mortem corneas, and this is in itself a restrictive factor as to the reliability of the picture of the normal regulation available to us.

A possibility of following variations in the corneal oedema was presented when an apparatus applicable for measurement of the thickness was discribed (Mishima & Hedbys 1968). Technical improvements have since occured (Ehlers & Kruse Hansen 1971, Ehlers & Sperling 1977). In 1968 Maurice described a specular microscope with which it is possible to examine corneal endothelial cells in vivo.

By this means it was possible to examine the connection between endothelium cells and corneal oedema (Bourne & Kaufman 1976). These examinations suggest that corneal oedema occurs when the number of endothelial cells become sufficiently low, but the mechanisms regulating the thickness of the normal cornea and the mechanisms responsible for the degeneration of the corneal endothelium are still unknown.

In 1 of patients with traumatic hyphaema who were *given no* antifibrinolytic treatment, the thickness of central *cornea* was followed with daily measurements. Simultaneously the serum content at activator *inhibitor* was measured after regular blood samplings after the trauma.

A connection in time was established between the reduction of the thickness of

treatment of traumatic hyphaema and following surgical intervention in the eye In this connection attention must be paid to the various drugs used in the treatment Acetylsalicylic acid is a commonly used drug in the treatment of painful conditions Menon (1970) and Moroz (1977) have shown that in vivo examination of humans this drug increases fibrinolytic activity Aspirin has a inhibiting effect on the aggregation of thrombocytes (O Brien 1968) Crawford et al (1975) demonstrated a significant increased frequency of secondary haemorrhages by traumatic hyphaema in patients treated with aspirin

No toxic injuries in humans by tranexamic acid have been described in the literature In this investigation a few patients have had a slightly increased peristaltic motion This did not necessitate any discontinuation of treatment No cases of deep vein thromboses occurred

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Fuchs' endothelial dystrophy (article IV)

A corneal oedema is found in patients with Fuchs endothelial dystrophy Doggert (1957) writes »At any rate I hope I have been able to convince you those who were not already convinced that Fuchs dystrophy is an important disease and it is assuredly a humbling thought for us all that in spite of research by generations of ophthalmologists in many lands the origin of this condition is still an enigma

Fuch s dystrophy is regarded as a primary disease in the corneal endothelium The condition becomes clinically manifest in elderly patients as a rule women (Doggart 1957) Fuchs (1910) was the first to describe the condition Vogt (1921) carried out slit lamp examinations of the disease and was the first to use the term Cornea guttata about the endothelial changes After this the disease was regarded as a primary affection of the corneal endothelium leading to an oedema af the corneal stroma and eventually to epithelial bullae Investigations on this disease have all been concentrated around the cornea and the corneal endothelium Many histologic and electron microscopic investigations on corneas in patients suffering from Fuchs dystrophy are available (Hogan et al 1974 Lorenzetti et al 1967) These investigations have found degenerative changes in the cytoplasma and enlargement of the intracellular compartment filled with hyaline deposits

The disease which has a progressive course leads to reduced visual acuity and pain and consequently needs treatment Many treatments have been attempted among them osmotheraphy (Luxenberg & Green 1971) dry air (Levenson 1973) conjunctival suturing (Gunderson 1958) contact lenses (Espy 1971 Gasset & Kaufman 1971) and pressure reducing treatment (Stocker 1965) The effect of these treatments is minimal and brief The surgical treatment with penetrating transplantation of cornea seems most effective (for a survey article see Levenson 1975)

Personal investigations

Material and methods

The material concisted of 15 women and 5 men suffering from Fuchs dystrophy Their average age was 65 4 (46–79 years of age) Most patients were referred for a corneal transplantation a few were also referred for a cataract At the time of confinement the thickness of central cornea was measured with a Haag Streit pachometer In our hands the method has a coefficient of variation of 1% Slit lamp examination and visual acuity were registered along with the subjective sensation of pain The patients were treated as out patients with tranexamic acid – 2 tablets x 3 daily and were controlled with the same examinations at intervals of approximately 1 month

Results

The period of observation varied from 3 to 16 months Nine patients were given intermittent treatment The shortest period of treatment was one month During the period of treatment the thickness of central cornea decreased in the case of discontinuation of treatment the thickness of the cornea increased Corneas with relatively pronounced oedema showed the greatest reduction of thickness Examples of curve tracings are shown in fig 3 1 20 (page 24)

From table VI the result concerning the visual acuity slit lamp examination and the subjective sensation of pain before and after the treatment is shown

Patient no.	Age Sex	Examination before treatment: Visual acuity	Slit lamp	Pain	Examination after treatment: Visual acuity	Slit lamp	Pain
		1	Epithelial bullae			[illegible] lae	
		[illegible]	Epithelial bullae		[illegible]	Epithelial [illegible] lae	
			Stromal oedema		[illegible]	Stromal oede	
			Epithelial			Epithelial [illegible] lae	
			Epithelial bullae			Epithelial bullae	
			[illegible] omal oedem			Stromal oedema	
	54		Stromal oedema			Stromal oedema	
		[illegible]	Epithelial		[illegible]	Epithelial lae	
		[illegible]	Epithelial			Epithel lae	
			[illegible] romal oede			[illegible] omal oede	

Patient no.	Age Sex	Examination before treatment: Visual acuity	Slit lamp	Pain	Examination after treatment: Visual acuity	Slit lamp	Pain
1	5[illegible] ♀		Epithelial bullae		1 0	[illegible] omal oede	
12		0 [illegible]	Epithelial bullae		1 [illegible]	Epithelial lae	
1	4[illegible] ♂		[illegible] omal oedema			[illegible] omal oedema	
14		0 [illegible] 0 [illegible]	Stromal oede			Stromal oedem	
1	7[illegible] ♀	[illegible]	Epithelial ullae		5 [illegible]	Epithelial lae	
16	[illegible]	0 0 05	Epithel bullae		2	Epithelial bullae	
1	72 ♂	0 0[illegible]	Epithelial ae			Epithelial	
18	6[illegible]		Epithelial lae		6	Epithelial lae	
1	72	0 5	Stromal oede		0 7	Stromal oedema	
20	6[illegible]	0 11	[illegible] omal oedem			Stromal oedema	

Table VI

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no	Age S	Examination before ment			Examination after treatment		
		ual ty	amp		ual ty	amp	
	[illegible]	pithe ial lae			Epithe ial lae		
	79	lgt	thelial bullae		lgt	Epithelial ae	
		67	om oedem		67	omal oedema	
			Epithel lae			Epithel ae	
			pithelial lae			Epithelial bu lae	
	50		omal oedema			o oedema	
			omal oedema			St omal oedema	
		[illegible]	pithel		lgt	Epithelial lae	
		lgt	pithelial		1	Epithelial lae	
			romal [illegible]			al [illegible]	

no	Age Sex	amination before atment			Exam nation aft me		
		ual ty	S mp		[illegible]	S amp	
	56 ♂		E helial bullae		3 9	St omal oedema	
2	♀	0 Hov	Epithelial lae		lgt	Epithelial bu ae	
13	46 ♂	1	S om oedema		0 1	S omal oedema	
		9	Stromal oedem		0 0	St omal oedema	
1	78 ♀	0 lgt	Epithelial bul ae		lgt	E helial bullae	
1		0 0 25	helial			Epithelial	
	72 ♂	0	Epithelial lae		0 (	Epithelial b lae	
		35	pithe ial		0 3	Epithelial lae	
	?	0 0	omal oedema		2 7	S omal oede	
20		0	S omal oedem		3 57	al oedema	

T bl VI

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Discussion

As already mentioned Fuchs endothelial dystrophy is regarded as a primary degenerative disease of the corneal endothelium and ind ed the disease occurs in elderly people and shows a progressive course Theoretically the disease might also be caused by endothelial cells being under constant influence from toxic drugs in the aqueous or from normally present drugs in abnormal concentrations Activation of the fibrinolytic system would lead to the formation of the proteolytic enzyme plasmin which might conceivably influence the corneal endothelium cells It is known that the degenerated endothelium cells release activators of the fibrinolytic system (Pandolfi & Astrup 1967) and hereby influence on the corneal endothelium would be increased Plasmin is likewise known to activate the complement system (both C_1 and C_3) (Nagasawa & Robert 1977 Lundh et al 1968 Soter et al 1975 Vogt et al 1975) a result of activation of this system is cell lysis The degenerative changes in patients with Fuchs dystrophy could also be explained via this system By administration of tranexamic acid both systems would be inhibited The results with transplantations of cornea support the theory that the degeneration of endothelium cells is due to a toxic influence Stocker & Irish (1969) followed patients transplanted for Fuchs dystrophy and patients transplanted for keratoconus and found that the endothelium of the donor disc in pati nts with Fuchs dystrophy had generated after 9 years in all cases In the patients suffering from keratoconus corneas were clear after 1J years Ehlers (1974) found that the maximum thickness of cornea measured after transplantations was greatest in patients with Fuchs dystrophy

These findings would be explicable if the composition of the chamber fluid in the Fuchs patients was toxic Lorenzetti et al (1967) using microscopy of patients of more than 40 years of age found that the endothelium had been degeneratively tran formed analagously with Fuchs dystrophy in 70% of the cases When elderly donors are used for transplantation it must be expected that some corneas with Fuchs dystrophy will be among the transplants Ehlers (1974) found that the maximum thickness after transplantations was largest when the donor was old but that the result in the long run was independent of ag of the donor These results sugg est that a normal donor disc transplanted to a cellularly environment will degenerate while a not to damaged donor disc transplanted to a normal environment will survive

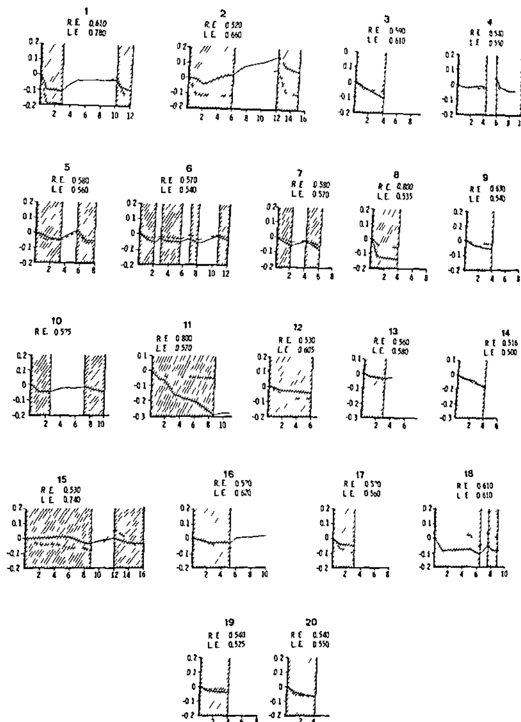


Fig. 3

Variations in central corneal thickness during treatment with tranexamic acid. All cases. Number of months. *Ordinate*: Relative central corneal thickness in mm. Hatched area: Period of treatment with tranexamic acid. R.E. and L.E.: Central corneal thickness before treatment. Unbroken line = R.E. Dotted line = L.E.

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Double blind investigation on the effect of tranexamic acid on th thickness of central cornea after cataract operations (article V)

The investigation on the effect of tranexamic acid on the thickness of corne patients with Fuchs dystrophy was not blind Bramsen & Steenbjerg (1 found that the content of various fibrinolytic factors in the aqueous humour f patients with Fuchs' dystrophy deviated from the content in the prim aqueous humour from patients with cataract The secondary aqueous hum from cataract patients however, was of a composition reminiscent of th patients with Fuchs dystrophy

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Personal investigations

Material and methods

The material consisted of 34 patients (22 women and 12 men) confined wit view to cataract operations The average age in the group treated w tranexamic acid was 65 3 + 2 6 years ($\bar{x} \pm$ sem) and in the control gr 68 3 ±1 9 years ($\bar{x} \pm$ sem) Solely patients with senile cataract as their only ocu disease were included in the investigation All operations were carried out by method described by Corydon & Mackensen (1978) and chymotrypsin was used

For a statistical calculation of the material sequence analysis was used a was difficult beforehand to determine how many patients were to be included the investigation Furthermore it was an advantage to be able to exclude a f patients because of operational complications

Tranexamic acid tablets (Cyclocapron®) and placebo tablets were produced the research department Kabi Stockholm Sweden and here divided into pa on glass containing tranexamic acid the other placebo The glasses were giv consecutive numbering and patient no 1 was given tablets from glass no 1 e The code was broken after patient no 18 no 32 and finally no 34 Nos 11 a 12 were left out because of surgical complications Tranexamic acid was giv from the day before operation until and including the 6th day The doses were mg/kg/day divided into 3 doses Preoperatively and the first six da

after the operation the thickne s of central cornea was measured daily with a Haag Streit pachometer as described by Ehlers & Sperling (1977) The intraocular pressure was measured on the day before the operation and from the 2nd to the 6th day following this Applanation tonometry was used as described by Goldmann

Curve sequences of the central thickness of cornea were registered in all patients in the po t surgical period of the cataract operations and from the e sequences it was decided which patients the investigators thought had been given tranexamic a id and which had been given placebo

Result

Fig 4 shows the result of the sequence analysis

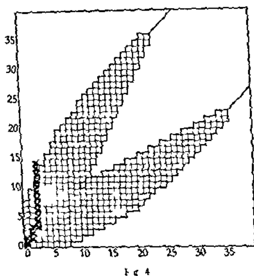


Fig 4

As already mentioned the investigators had estimated from each individual curve sequence which patients had b en given tranexamic acid and this result w is compared to the code kept at Kabi Stockholm As it appears it was possible in 16 pairs to reach a significant difference between the group treated with tranexamic acid and the one treated with placebo as there was accordance in 14 out of 16 pairs The average curve sequence of the thickness of central cornea within the two groups is illustrated in fig 5 The effect of the corresponding non operated eve is illustrated in fig 6

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Discussion

Investigation of the various factors within the fibrinolyctic system and C_3 complement within the complement system in patients with Fuchs dystrophy and in patients with cataract showed that the aqueous humour in patients with Fuchs dystrophy was of a composition with largely corresponded to the secondary aqueous humour in cataract patients (Bramsen & Steenbjerg 1979)

After cataract operations secondary aqueous humour occurs and this in connection with the trauma to the cornea must be supposed to lead to a corneal oedema In this investigation the trauma must be identical to the two groups and the difference in the thicknesses of the central corneae in the treated and the untreated groups respectively must be supposed to be due to differences in the composition of the secondary aqueous humour It is not yet known what factors are of importance for the development of the oedema

Double blind investigation on the effect of tranexamic acid on the intraocular pressure after operations for glaucoma simplex (article VI)

The above mentioned investigation showed no significant difference between the intraocular tension in patients treated with tranexamic acid or placebo Pandolfi & Kwaan (1967) showed that fibrinolytically active substances were found in human chamber angles This fibrinolysis localised at the outflow of aqueous humour from the anterior chamber might be influential in the regulation of the intraocular tension as an inhibiting of fibrinolysis might conceivably increase the tension and an activating decrease it Corresponding thoughts have been made about hyaluronidase Zimmerman (1957) found that hyaluronidases sensitive mucopolysaccharides were present in the human intra trabecular space Barany & Scotchbrook (1954) fond that infusion of testicular hyaluronidases into dead calves eyes reduced the outflow resistance by half Melton & De Ville (1960) also examined the outflow resistance after infusion of hyaluronidases and found different results with differenct species Pandolfi (1967) carried out perfusion examinations in vitro with plasmin and urokinases on monkeys eyes and found that plasmin reduced the outflow resistance while urokinases had no effect Saiduzzafar (1970) found that the outflow resistance was incrased when tranexamic acid was injected into the anterior chamber of monkeys The intraocular pressure is known to influence the thickness of central cornea (Ehlers 1970) furthermore the thickness of central cornea affects the measurements of the intraocular pressure with the Goldmann applanation tonometer (Ehlers et al 1975) If a universal fibrinolytic treatment is effective on the intraocular pressure in humans this might possibly explain the influence on the thickness of central

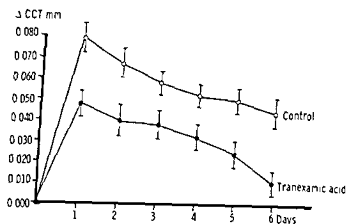


Fig 5

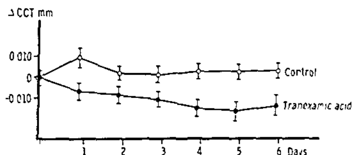


Fig 6

Table VII shows that tranexamic acid had no effect on the intraocular pressure in neither the operated eye nor the corresponding one

Intraocular pressure measured by applanation tonometry No correction for changes in *the thickness of cornea Values given as x̄ ± sem Number of eyes in each group = 16*

Intraocular pressure after cataract extraction

	Operated eye treated with *tranexamic acid*	Control	Contralateral eye treated with *tranexamic with*	Control
Preoperatively	14 6 ±0 94	12 8 ±0 74	14 9 ±0 98	12 3 ±0 77
2 postoperative day	13 1 ±1 12	14 5 ±1 73	15 4 ±0 94	13 5 ±0 78
3 postoperative day	15 1 ±1 46	14 1 ±1 95	14 7 ±0 79	13 9 ±0 52
4 postoperative day	13 1 ±1 12	13 3 ±0 94	13 9 ±0 78	14 3 ±0 48
5 postoperative day	15 36 ±1 72	14 3 ±0 80	15 1 ±0 84	14 0 ±0 52
6 postoperative day	13 8 ±0 80	13 4 ±0 58	14 6 ±0 79	14 2 ±0 60

Table VII

D s uss on

Investigation of the various factors within the fibrinolyctic system and C_3 complement within the complement system in patients with Fuchs dystrophy and in patients with cataract showed that the aqueous humour in patients with Fuchs dystrophy was of a composition with largely corresponded to the secondary aqueous humour in cataract patients (Bramsen & Steenbjerg 1979)

After cataract operations secondary aqueous humour occurs and this in connection with the trauma to the cornea must be supposed to lead to a corneal oedema In this investigation the trauma must be identical to the two groups and the difference in the thicknesses of the central corneae in the treated and the untreated groups respectively must be supposed to be due to differences in the composition of the secondary aqueous humour It is not yet known what factors are of importance for the development of the oedema

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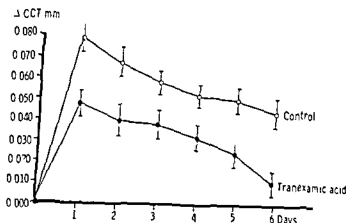


Fig 5

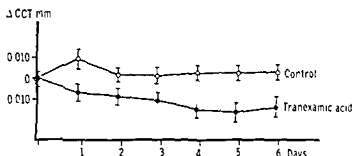


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Intraocular pressure measured by applanation tonometry No correction for changes in the thickness of cornea Values given as $\bar{x} \pm$ sem Number of eyes in each group = 16

Intraocular pressure after cataract extraction

	Operated eye treated with tranexamic acid	Control	Contralateral eye treated with tranexamic with	Control
Preoperatively	14 6 ±0 94	12 8 ±0 74	14 9 ±0 98	12 3 ±0 77
2 postoperative day	13 1 ±1 12	14 5 ±1 73	15 4 ±0 94	13 5 ±0 78
3 postoperative day	15 1 ±1 46	14 1 ±1 95	14 7 ±0 79	13 9 ±0 52
4 postoperative day	13 1 ±1 12	13 3 ±0 94	13 9 ±0 78	14 3 ±0 48
5 postoperative day	15 36 ±1 72	14 3 ±0 80	15 1 ±0 84	14 0 ±0 52
6 postoperative day	13 8 ±0 80	13 4 ±0 58	14 6 ±0 79	14 2 ±0 60

Table VII

Result

The result as regards the thickness of central cornea appears in fig 7

As in the double blind investigation on the thickness of the cornea after cataract operations it was determined from the curve sequence of the thickness of central cornea in each patient which had been given tranexamic acid and after comparison with the code fig 7 was constructed

Fig 8 shows the averaged changes in the intraocular pressure on the operated eye during the first 5 days after trabeculectomy ($\bar{x} \pm$ sem) The group treated with tranexamic acid shows a somewhat higher pressure in the postoperative period than the placebo group At none of the measuring times is the difference statistically significant

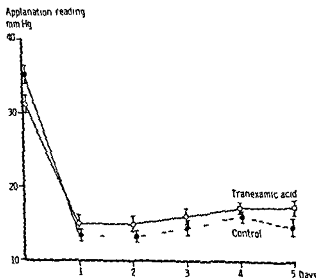


Fig 8

Fig 9 illustrates the changes in the intraocular pressure in the corresponding non operated eye Also here the group treated with tranexamic acid hows a somewhat higher tension

Discussion

The investigation has found no influence of universal antifibrinolytic treatment on the intraocular pressure in patients with glaucoma simplex The treatment does not seem to influence the filtration af er the operation

cornea Accordingly a double blind investigation on the effect of tranexamic acid on the intraocular pressure in patients with glaucoma simplex was carried out

Personal investigations

Material and methods

The material consisted of 28 patients (12 women and 16 men) Only patients with glaucoma simplex were included in the investigation The average age of the group treated with tranexamic acid was 68 6 ±3,2 years ($\bar{x}$ ± sem) that of the control group 63,9 ±3 6 years All operations were carried out as trabeculectomies The tranexamic acid and placebo tablets were delivered by the research department Kabi Stockholm The glasses with tablets were divided into pairs one containing tranexamic acid the other placebo The glasses were numbered in succession and patient no 1 had tablets from glass no 1 etc The code was broken after patient no 28 One pair was excluded from the investigation before the code was broken because of surgical complications Tranexamic acid was given in the form of tablets 75 mg/kg/day distributed into 3 doses The treatment started the day before the operation and was continued until and including the 5th day Before the operation all patients were subjected to a slit lamp examination opthalmoscopy gonioscopy and perimetry a m Goldmann The thickness of central cornea was measured daily from the day before the operation and throughout the 5 postoperative days The measurement was carried out by a Haag Streit pachometer as described above The intraocular tension was likewise measured the day before the operation and the following 5 days be means of applanation tonometry a m Goldmann

Sequence analysis was used for statistical evaluation on the effect on the thickness of central cornea

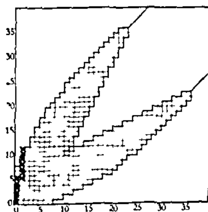


fig 7

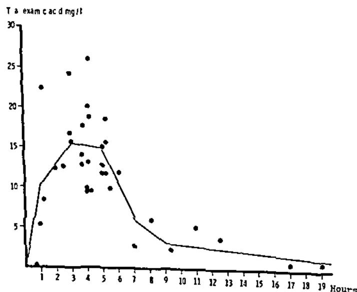
Personal investigations

Material and methods

The material consisted of 37 patients who were hospitalized for operation for cataract The average age was 67 5 years with a deviation from 50 to 83 years Only patients with a normal serum creatinine were included

Thirty five of the patients were given peroral tranexamic acid 25 mg/kg at varying times before the operation (45 minutes to 19 hours) The cataract operation was commenced by aspiration of about 200 µl aqueous humour and immediately thereafter a venal puncture was carried out with an extraction of blood for a determination of the concentration of tranexamic acid in the serum Aqueous humour and serum were frozen down to 18° celsius and sent to the research department Kabi Stockholm The analyses were here made with gas chromotography as described by Vessmann & Stromberg (1975) In two patients the amount of aqueous humour was insufficient for determination Two patients were treated perorally with tranexamic acid 25 mg/kg/day x 3 for 3 days before the operation which was undertaken 8 hours after the intake of the last tablet

There were considerable differences in the serum concentrations and in the aqueous humour concentrations An average curve was drawn in the following way The average of all values between 0 2 hours was marked as value corresponding to 1 hour The average of the values between 2 4 hours as value corresponding to 3 hours etc



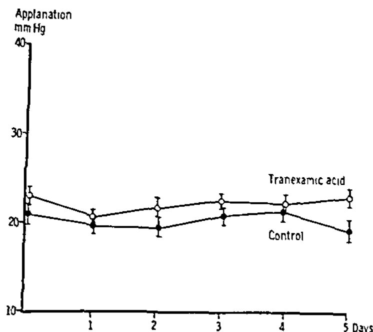


Fig 9

Variations in the intraocular pressure do not accordingly seem to offer an explanation of the effect of tranexamic acid on the thickness of central cornea

As mentioned Pandolfi (1967) found that local fluctuations of fibrinolysis could affect the outflow resistance in monkeys The lack of effect on the intraocular pressure in the present investigation could be due to an inability of tranexamic acid to pass through the blood aqueous humour barrier

The content of tranexamic acid in the aqueous humour after peroral administration (article VII)

The literature shows no investigations on the concentration of tranexamic acid in the anterior chamber

Davson (1956) has pointed out the similarities between the composition and formation of cerebrospinal humour and aqueous humour Tovi & Thulin (1972) found that tranexamic acid was capable of passing from blood into the cerebrospinal fluid and that an increase in the concentration took place after repeated injections

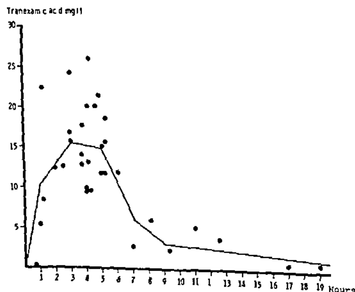
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Results

Fig 10 shows the serum concentrations after a single peroral dose of tranexamic acid at varying times after intake The maximum concentation (15 44 mg/l) is reached after 3 hours After 19 hours tranexamic acid is still found in the serum

Fig 11 shows the results of the determination of the aqueous humour concentrations The highest concentration is reached after 3 hours (1 62 mg/l) After this the fall in the concentration is very slow so that the 19 hour value does not vary much from the 3 hour value

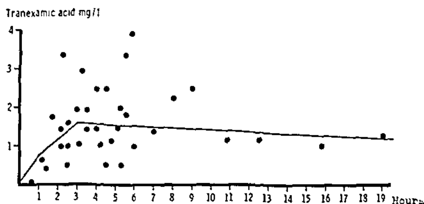


Fig 11

In the two patients who had been given tranexamic acid 25 mg/kg × 3 for three days aqueous humour concentrations of 2 3 mg/l were found in both patients 8 hours after the last intake This value is about 40% above the average value after a single oral intake

Discussion

Tranexamic acid is capable of passing the blood aqueous humour barrier and during the first 5 hours after oral intake the concentration is about 10% of the serum concentration It is possible that an increase in the concentration takes place after repeated intake Tovi & Thulin (1972) found that a concentration of 0 3 mg/l in the cerebrospinal fluid was capable of reducing the content of FDP in the spinal fluid so that the concentrations reached in the anterior chamber must be supposed to be able to inhibit fibrinolysis

The effect of urokinases on the thickness of central cornea and on corpus vitreus haemorrhages (article VIII)

The already mentioned investigations above have shown that antifibrinolytic treatment with tranexamic acid is capable of reducing a corneal oedema and possibly reduce the thickness of the normal cornea Judging from these observations the fibrinolytic system might conceivably be involved in the regulation of the thickness of the cornea A fibrinolysis activating treatment should in that case lead to a corneal oedema

Urokinase is a naturally present activator of the fibrinolytic system This drug has been used in the treatment of corpus vitreous haemorrhages Chapman Smith & Crock (1977) found that after injections of urokinase into the corpus vitreum corneal oedema occurred with folds in Descemets membrane

Morten & Turnbull (1964) examined the effect of fibrinolysis (plasmin) on bovine cornea after infusion into the anterior chamber and found that an infusion of 5000 units/ml destroyed 60% of the endothelial cells 10 000 units/ml destroyed 90% of the endothelial cells and after this the cornea became cloudy These investigations show that fibrinolytic activators or fibrinolysis are destructive for endothelial cells

Personal investigations

Material and methods

The material consisted of 13 patients with corpus haemorrhages Table VIII gives the causes of the haemorrhages Furthermore the distribution in age and sex among the 13 patients is shown

Cause of haemorrhage and capacity	Number of females	Age range	Number of males	Age range
Diabetes	2	68 to 74 years	6	26 to 47 years
Trauma	1	74	3	22 to 35 years
Eales disease	0		1	26 years

Table VIII

The treatment consisted of injection of urokinase 25 000 Plough units (Leo pharmaceutical products Denmark) dissolved in 0 3 ml of distilled water The injection was made by means of a 0 6 mm hypodermic needle which after

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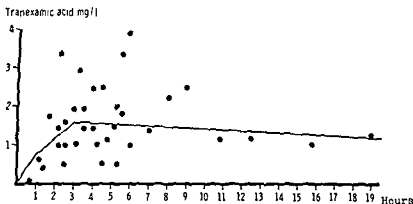


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diathermy and a 2 3 mm incision of sclera in pars plana in the lower temporal quadrant was directed towards the centre of corpus vitreum Immediately after the operation 500 mg of acetazolamide were given and in the following 7 days the eye was treated locally with atropine 1% × 2 and chloramphenicol ointment × 3 daily Two of the patients were treated with the antifibrinolytic drug tranexamic acid for 8 days The treatment started one day before the operation and the dose was 75 mg/kg distributed over 3 daily doses

Before the operation all patients were subjected to slit lamp examination ophthalmoscopy measurement of visual acuity measurement of intraocular tension a m Goldmann and measurement of the thickness of central cornea as described above

The patients stayed at hospital for 7 days and were later controlled every 7th day The thickness of central cornea was measured daily during the confinement

Results

The effect on the corpus haemorrhages and the visual acuity in the individual patients is shown in Table IX Patients no 7 and 8 were given two injections of urokinase Patients no 6 and 13 were treated with tranexamic acid

HM = hand movements FC = finger counting + L = perception of light + L + P = perception + projection of light + + + = retina not visible by ophthalmoscopy + + = retina just visible by ophthalmoscopy + = diminitive vitreous opacities

Patient No	Diagnoses	Before treatment: Visual acuity	Before treatment: Vitreous haemorrhages	After treatment: Visual acuity	After treatment: Vitreous haemorrhages	Period of follow up (months)
1	Diabetes	+ L + P	+ + +	FC	+ +	5
2	Diabetes	+ L	+ +	+ L	+	2
3	Diabetes	+ L + P	+ + +	+ L + P	+ + +	2
4	Diabetes	HM	+ + +	HM	+	4
5	Diabetes	HM	+ + +	HM	+ + +	1
6	Diabetes	+ L	+ +	+ L	+	4
7	Diabetes	+ L	+ + +	HM	+ +	7
8	Diabetes	HM	+ + +	FC	+ +	6
9	Trauma	+ L	+ +	+ L	+ +	4
10	Trauma	+ L + P	+ + +	+ L + P	+	5
11	Trauma	+ L	+ + +	+ L	+ +	3
12	Trauma	0 05	+ +	0 05	+ +	3
13	Eales Disease	+ L	+ + +	+ L	+ + +	5

Table IX

The variations in the thickness of central cornea in the operated eye is illustrated n fig 12 ($\bar{x} \pm$ sem)

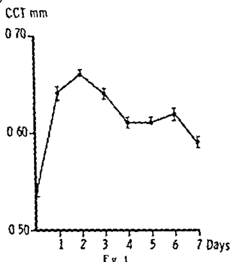


Fig 1

Th maximum thickness of the cornea is rea hed on the 2nd day and on the 6th d y a secondary increase in the thickness of central cornea appears In the two patients treated with tranexamic acid corneal oedema also appeared with a maximum thickness on the ?nd day but the secondary increase in thickness failed to appear Fig 13 shows the changes in the thickness of central cornea in the correspondong non operated eye ($\bar{x} \pm$ sem)

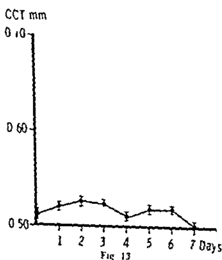


Fig 13

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Patient No	Diagnoses	Before treatment: Visual acuity	Before treatment: Vitreous haemorrhages	After treatment: Visual acuity	After treatment: Vitreous haemorrhages	Period of follow up (months)
1	Diabetes	+ L + P	+ + +	FC	+ +	5
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3	Diabetes	+ L + P	+ + +	+ L + P	+ + +	2
4	Diabetes	HM	+ + +	HM	+	4
5	Diabetes	HM	+ + +	HM	+ + +	1
6	Diabetes	+ L	+ +	+ L	+	4
7	Diabetes	+ L	+ + +	HM	+ +	7
8	Diabetes	HM	+ + +	FC	+ +	6
9	Trauma	+ L	+ +	+ L	+ +	4
10	Trauma	+ L + P	+ + +	+ L + P	+	5
11	Trauma	+ L	+ + +	+ L	+ +	3
12	Trauma	0 05	+ +	0 05	+ +	3
13	Eales Disease	+ L	+ + +	+ L	+ + +	5

Table IX

cornea was measured by the method described above The thickness of the donor disc was measured regularly during the 14 days in which the patients were confined after the transplantation and in most cases daily

The material was divided into 6 groups according to ocular disease which had lead to the transplantation 1) 66 cases of keratitis 2) 38 cases of keratoconus 3) 23 cases of Fuchs endothelial dystrophy 4) 12 cases of stromal dystrophy 5) 16 cases of cauterization or mechanical damage and 6) 17 cases in which treatment with tranexamic acid was commenced before the 3rd day after transplantation The dose of tranexamic acid was 75 mg/kg distributed over 3 daily doses

The 17 cases consisted of 9 patients with keratitis 2 with Fuchs dystrophy 4 with stromal dystrophy and 2 cases with mechanical damage The average donor age and the average donor disc age of the individual groups were calculated The result is shown in Table X A variance analysis found no significant difference between the donor age and the donor disc age in the various groups

Diagnostic group	No	Donor age (years) $\bar{x} \pm$ sem	Graft age (min) $\bar{x} \pm$ sem
Keratitis	66	44 93 ±2 13	363 91 ±42 39
Keratoconus	38	39 38 ±3 12	317 15 ±37 75
Fuchs dystrophy	23	40 55 ±2 90	395 74 ±76 60
Stromal dystrophy	12	40 83 ±5 52	325 00 ±110 74
Corrosion or mechanical lesion	16	45 24 ±5 29	346 47 ±72 79
Tranexamic acid treated	17	44 59 ±4 22	235 94 ±35 27

Table X

Diagnosis	No of cases	Steady fall	Secondary increase 4th to 7th day
Keratitis	66	17	49
Keratoconus	38	30	8
Fuchs dystrophy	23	10	13
Stromal dystrophy	12	6	6
Mechanical lesion or corrosion	16	2	14
Tranexamic acid treatment	17	14	3
Total	172	79	93

Table XI

The fluctuations here are smaller but show the same tendency

Discussion

Injection of urokinase into the corpus vitreum leads to a corneal oedema The operational trauma here is minimal and the *anterior chamber is not opened in* connection with the operation Morten & Turnbull (1964) examined the effect of the fibrinolysis activating drug fibrinolysin on rabbits eyes when this drug was injected into the anterior chamber and also found a pronounced corneal oedema the size of which was dependent on the concentration of the firbrinolysin Jukofski (1951) *demonstrated corneal oedemae in humans* after treatment of haemorrhages in the anterior chamber with streptokinase It must be added that the urokinase used in this investigation contains other proteolytic substances which may be responsible for the development of the corneal oedema

As shown in fig 13 fluctuations are found in the thickness of central cornea in *the corresponding non operated eye* and *these fluctuations correspond in time* to those of the operated eye One possible explanation could be that the injection of urokinase was capable of affecting the fibrinolysis of the entire organism

Early postoperative fluctuations in the thickness of central cornea after penetrating keratoplasty (article IX)

It is well known that patients with Fuchs dystrophy when operated upon for cataract develop a vigorous corneal oedema in the postopertive period and often remain corneally oedematous One explanation *of this may be that the corneal* endothelial cells in these patients are already degeneratively transformed Another explanation of the corneal oedema could be that the development accordingly is a deficient regulating mechanism

A model to examine the regulating mechanism after surgical intervention would be to examine *the thickness of central cornea in the postoperative period* of transplantations as one must in such cases expect different groups of patients to recieve on average identical corneas

Personal investigations

Material and methods

The material consisted of 172 patients who were subjected to a penetrating cor neal transplantation in the period from 1 1 1973 to 1 4 1978 The operational technique has already been described (Ehlers 1974) The thickness of the central

cornea was measured by the method described above The thickness of the donor disc was measured regularly during the 14 days in which the patients were confined after the transplantation and in most cases daily

The material was divided into 6 groups according to ocular disease which had lead to the transplantation 1) 66 cases of keratitis 2) 38 cases of keratoconus 3) 23 cases of Fuchs endothelial dystrophy 4) 12 cases of stromal dystrophy 5) 16 cases of cauterization or mechanical damage and 6) 17 cases in which treatment with tranexamic acid was commenced before the 3rd day after transplantation The dose of tranexamic acid was 75 mg/kg distributed over 3 daily doses

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Table X

Diagnosis	No of cases	Steady fall	Secondary increase 4th to 7th day
Keratitis	66	17	49
Keratoconus	38	30	8
Fuchs dystrophy	23	10	13
Stromal dystrophy	12	6	6
Mechanical lesion or corrosion	16	2	14
Tranexamic acid treatment	17	14	3
Total	172	79	93

Table XI

The fluctuations here are smaller but show the same tendency

Discussion

Injection of urokinase into the corpus vitreum leads to a corneal oedema The operational trauma here is minimal and the anterior chamber is not opened in connection with the operation Morten & Turnbull (1964) examined the effect of the fibrinolysis activating drug fibrinolysin on rabbits eyes when this drug was injected into the anterior chamber and also found a pronounced corneal oedema the size of which was dependent on the concentration of the firbrinolysin Jukofski (1951) demonstrated corneal oedemae in humans after treatment of haemorrhages in the anterior chamber with streptokinase It must be added that the urokinase used in this investigation contains other proteolytic substances which may be responsible for the development of the corneal oedema

As shown in fig 13 fluctuations are found in the thickness of central cornea in the corresponding non operated eye and these fluctuations correspond in time to those of the operated eye One possible explanation could be that the injection of urokinase was capable of affecting the fibrinolysis of the entire organism

Early postoperative fluctuations in the thickness of central cornea *after penetrating keratoplasty (article IX)*

It is well known that patients with Fuchs dystrophy when operated upon for cataract develop a vigorous corneal oedema in the postopertive period and often remain corneally oedematous One explanation of this may be that the corneal endothelial cells in these patients are already degeneratively transformed Another explanation of the corneal oedema could be that the development accordingly is a deficient regulating mechanism

A model to examine the regulating mechanism after *surgical intervention* would be to examine the thickness of central cornea in the postoperative period of transplantations as one must in such cases expect different groups of patients to recieve on average identical corneas

Personal investigations

Material and methods

The material consisted of 172 patients who were subjected to a penetrating corneal transplantation in the period from *1 1 1973 to 1 4 1978 The operational* technique has already been described (Ehlers 1974) The thickness of the central

cornea was measured by the method described above The thickness of the donor disc was measured regularly during the 14 days in which the patients were confined after the transplantation and in most cases daily

The material was divided into 6 groups according to ocular disease which had lead to the transplantation 1) 66 cases of keratitis 2) 38 cases of keratoconus 3) 23 cases of Fuchs endothelial dystrophy 4) 12 cases of stromal dystrophy 5) 16 cases of cauterization or mechanical damage and 6) 17 cases in which treatment with tranexamic acid was commenced before the 3rd day after transplantation The dose of tranexamic acid was 75 mg/kg distributed over 3 daily doses

The 17 cases consisted of 9 patients with keratitis 2 with Fuchs dystrophy 4 with stromal dystrophy and 2 cases with mechanical damage The average donor age and the average donor disc age of the individual groups were calculated The result is shown in Table X A variance analysis found no significant difference between the donor age and the donor disc age in the various groups

Diagnostic group	No	Donor age (years) x ± sem	Graft age (min) x̄ ± sem
Keratitis	66	44 93 ±2 13	363 91 ±42 39
Keratoconus	38	39 38 ±3 12	317 15 ±37 75
Fuchs dystrophy	23	40 55 ±2 90	395 74 ±76 60
Stromal dystrophy	12	40 83 ±5 52	325 00 ±110 74
Corrosion or mechanical lesion	16	45 24 ±5 29	346 47 ±72 79
Tranexamic acid treated	17	44 59 ±4 22	235 94 ±35 27

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Table XI

For all patients curve sequences of the variations in the thickness of central cornea were drawn in the postoperative period of the transplantation. Furthermore, average curves were calculated for the development within the above mentioned 6 groups ($\bar{x} \pm$ sem). In patients with stromal dystrophies and cauterizations and mechanical lesions the measurements in the last days were too few for a calculation of daily averages, wherefore the average of these measurements is marked as the value on the 11th day.

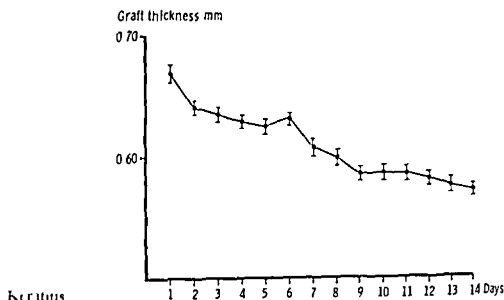


Fig. 14

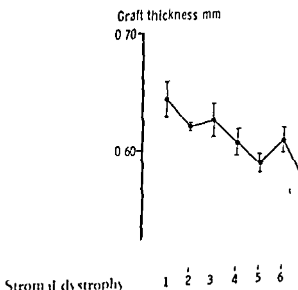


Fig. 15

Results

The average curves of the 7 groups are seen in Fig 14 19 Three characteristic curve sequences appear The groups with keratitis stromal dystrophies and cauterizations and mechanical damages show a secondary increase of thickness on the 6th day after the trauma (figs 14 15 and 16) The group with keratoconus and the one treated with tranexamic acid lack the secondary increase on the 6th day (figs 17 and 18) Patients with Fuchs dystrophy (fig 19) do not reach maximum thickness of the cornea until the 3rd postoperative day

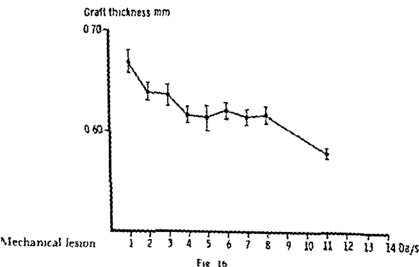


Fig 16

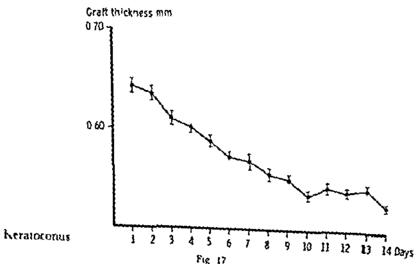
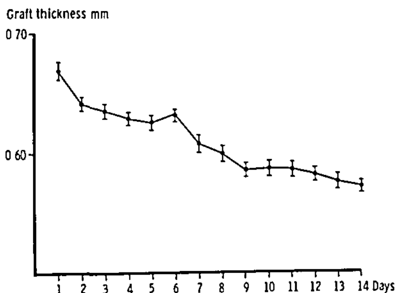


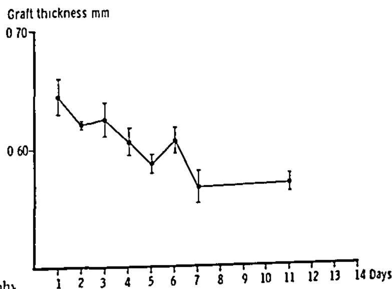
Fig 17

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Keratitis

Fig 14



Stromal dystrophy

Fig 15

Discussion

Ehlers (1974) in a postoperative examination of 70 cornea transplanted patients demonstrated that two different curve sequences appeared in the time after the operation One showed a constant fall the other showed a secondary increase in thickne s about one week after transplantation The present investigation has confirmed these two sequences Patients with keratitis stromal dystrophies and cauterizations and mechanical lesions show a secondary increase in the thickness of the central cornea between the 4th and the 7th day while patients with keratoconus lack this secondary increase in thickness Patients with Fuchs dystr phy show a completely different development of thickness characterised by an increase in thickness during the first postoperative days Patients treated with tranexamic acid show a curve sequence almost identical with that of the keratoconus patients It must be added that none of the patients t eated with tranexamic acid suffered from keratoconus

As the age of the donor and the age of the transplant did not deviate in the individual groups it is natural to seek an explanation in the different *responses* to surgical interventions in the various groups

As already mentioned investigations exist on fluctuations in fibrinolytic activity after traumas (Ygge 1970 Rammer & Salden 1970 Knight et al 1977) These investigations show that the inhibitors are increased in the serum in the days following a surgical intervention and that du ing the same days the fibrinol tic activity falls After about one week the content of inhibitors decreases and fibrinolysis is simultaneously increa ed

These fluctuations are understandable After a trauma fibrin *is formed in the* wound and this fibrin stabilises the wound and *forms* a skeleton for collagen synthesis which starts when fibrin is decomposed after about one week Reme & Wurmer (1974) showed that fibrin is formed in *iris wounds* It begins to disappear on the 5th day and is completely re olved 7 *days* after the lesion In terms of time the secondary increase in the thickness of the cornea could be explained by fluctuations in *fibrinolysis* and the circumstance that patients treated with *tranexamic* acid lack the secondary *increase* also speaks in favour of a fibrinolytic genesis

From the 172 curve sequences it was calculated how many patients showed a constant fall and how many showed a secondary increase in thickness between the 4th and the 7th postoperative day The result appears in Table XI Among the 66 keratitis patients 49 showed a secondary increase in thickness while only 8 out of 38 patients with keratoconus produce such a secondary incrase in thickness In the group treated with tranexamic acid a secondary increase in thickness appeared in 3 out of 17 patients On calculation of the figures by an χ test the significance appears (P<0 001)

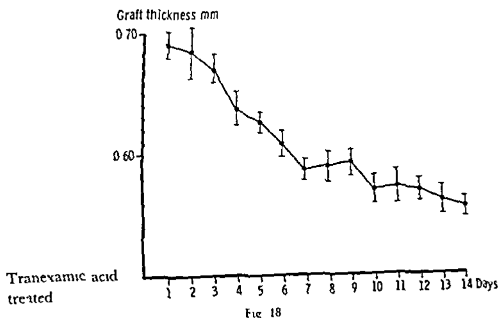


Fig 18

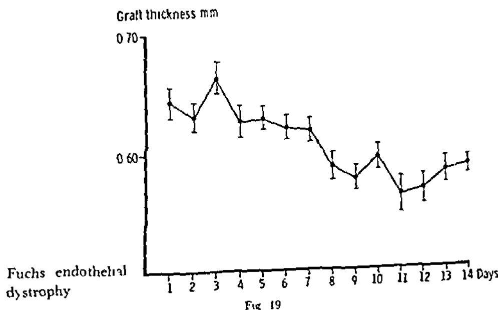


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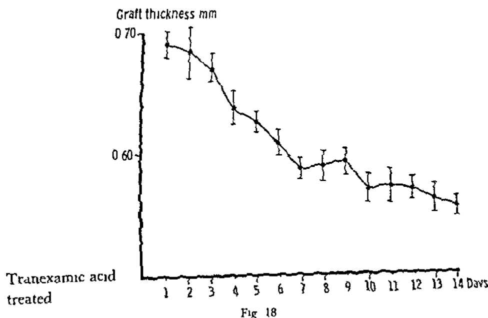


Fig 18

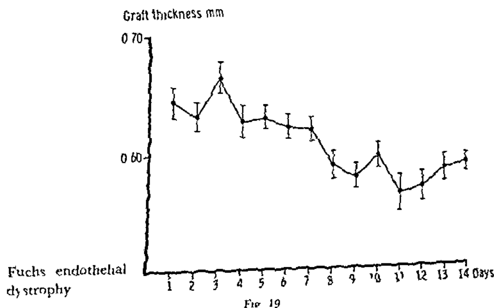


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Chapter IV

CONCLUDING REMARKS

The investigation on the effect of tranexamic acid on traumatic hyphaema has not been carried out as a double blind study. Before this treatment was started it was calculated that a double blind investigation would take about 7 years if 40 patients were confined for one year and the frequency of secondary haemorrhage was 6%. In the first investigation on the effect of tranexamic acid on traumatic hyphaema (article I) a calculus of probability was made on the results achieved. 135 patients from the period 1965-68 with 9 secondary haemorrhages were compared to 72 patients from the period 1975 with 1 secondary haemorrhage. Through such a calculation a probability of 95.8% was found in favour of the effectiveness of a treatment with an antifibrinolytic drug. The materials are not from the same period and so are not statistically comparable, but the calculations nevertheless indicate an effect of the treatment and were made as it was the first time that a treatment of traumatic hyphaema with tranexamic acid was published.

All in all 310 patients with traumatic hyphaemas have been treated with tranexamic acid, and one secondary haemorrhage has occurred in a patient who was also confined to bed. 153 patients not confined to bed have been treated at the department and 88 patients have been treated ambulatorily, and in these two last mentioned groups no secondary haemorrhage have occurred. During an antifibrinolytic treatment then bed rest and confinement seem unnecessary. An out-patient treatment, however, must be expected to produce some secondary haemorrhages, as some patients will fail to take their tablets or take them irregularly.

The investigations on the activator inhibitor content in the serum in the postoperative period of traumatic hyphaema have only been carried out on 4 patients. This investigation must necessarily be carried out on patients who are not receiving antifibrinolytic treatment and for this reason, among others, the material has not been extended as these patients are then exposed to a greater risk of secondary haemorrhages. It would, however, be interesting to examine whether secondary haemorrhages occur in patients who, following the trauma, are incapable of inhibiting the fibrinolysis sufficiently. It is possible that further

investigations might find a blood factor indicating whether it is necessary to use antifibrinolytic drugs or whether the patient himself can inhibit the fibrinolysis sufficiently

Tranexamic acid reduces the thickness of the central cornea in cases of corneal oedema This is shown in a double blind investigation on corneal oedema after cataract operations and after operations for glaucoma simplex In patients with Fuchs endothelial dystrophy an oedema reducing effect of tranexamic acid has likewise been found

Nothing has been proved about the causation behind this oedema reducing effect The effect may due to an inhibition of the fibrinolytic system locally or universally Another possibility is an effect via the complement system as tranexamic acid influences the activity of this system Finally it is possible that the effect of this drug is due to a displacement of the normal amino acid composition in the anterior chamber as tranexamic acid is a synthetic neutral amino acid

In patients who have been subjected to a penetrating corneal transplantation a varying development of the thickness of the cornea has been found in the postoperative period of the transplantation among different recipient groups In patients with e g keratitis a secondary increase in thickness has been found between the 4th and the 7th day after the operation whereas patients with keratoconus after the transplantation show a constant fall in the development of the thickness of the cornea If keratitis patients are treated with tranexamic acid the secondary increase of thickness disappears and the curve of the thickness of central cornea achieves a development resembling that of keratoconus patients These circumstances may be due to differens fibrinolytic responses to traumas in the individual groups a possibility now under investigation (Bramsen & Stenbjerg 1980)

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Summarised results

310 patients with traumatic hyphaema have been treated with tranexamic acid perorally in doses of 25 mg/kg three times daily One secondary haemorrhage has occurred (0 3°~) Beside the antifibrinolytic treatment 72 patients were

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310 patients with traumatic hyphaema have been treated with tranexamic acid perorally in doses of 25 mg/kg three times daily One secondary haemorrhage has occurred (0 32%) Beside the antifibrinolytic treatment 72 patients were

treated with bed rest and stenopaeic spectacles 153 patients were treated at the department but not confined to bed and 85 patients were treated on an out patient basis No secondary haemorrhages occurred within the two last mentioned groups

Peroral treatment with tranexamic acid in the abovementioned doses of patients with Fuchs dystrophy reduced the thickness of central cornea

Double blind investigations on corneal oedemas developed after operations for cataract and glaucoma simplex have shown that administration of tranexamic acid to patients reduces the thickness of the central cornea in the postoperative period Tranexamic acid does not seem to influence the intraocular pressure

The investigations on the concentration of tranexamic acid in the serum and in the aqueous humour show that the highest concentration is reached after about 3 hours The drug is capable of passing the blood aqueous humour barrier and the content in the aqueous humour is about 10% of the serum concentration

Injection of urokinase into the corpus vitreum with the purpose of increasing the resorption of a corpus vitreous haemorrhage leads to a corneal oedema in both the treated and the corresponding non operated eye

In postoperative examinations of the thickness of the central cornea in transplanted patients three characteristic curve sequences have been found Patients transplanted because of keratitis stromal dystrophies and cauterizations and mechanical damages show a secondary increase in thickness on the 6th day after the operation This secondary increase in thickness can be prevented or reduced by peroral administration of tranexamic acid Patients with Fuchs dystrophy do not reach the maximum thickness of the cornea until the 3rd postoperative day Patients with keratoconus show a steadily falling thickness with a maximum on the 1st postoperative day and no secondary increase in thickness

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treated with bed rest and stenopaeic spectacles 153 patients were treated at the department but not confined to bed and 85 patients were treated on an out patient basis No secondary haemorrhages occurred within the two last mentioned groups

Peroral treatment with tranexamic acid in the abovementioned doses of patients with Fuchs dystrophy reduced the thickness of central cornea

Double blind investigations on corneal oedemas developed after operations for cataract and glaucoma simplex have shown that administration of tranexamic acid to patients reduces the thickness of the central cornea in the postoperative period Tranexamic acid does not seem to influence the intraocular pressure

The investigations on the concentration of tranexamic acid in the serum and in the aqueous humour show that the highest concentration is reached after about 3 hours The drug is capable of passing the blood aqueous humour barrier and the content in the aqueous humour is about 10% of the serum concentration

Injection of urokinase into the corpus vitreum with the purpose of increasing the resorption of a corpus vitreous haemorrhage leads to a corneal oedema in both the treated and the corresponding non operated eye

In postoperative examinations of the thickness of the central cornea in transplanted patients three characteristic curve sequences have been found Patients transplanted because of keratitis stromal dystrophies and cauterizations and mechanical damages show a secondary increase in thickness on the 6th day after the operation This secondary increase in thickness can be prevented or reduced by peroral administration of tranexamic acid Patients with Fuchs dystrophy do not reach the maximum thickness of the cornea until the 3rd postoperative day Patients with keratoconus show a steadily falling thickness with a maximum on the 1st postoperative day and no secondary increase in thickness

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SUPPLEMENTUM 144

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A K. K. K. LUNDSGAARD EDI COEPTA

Response of Human Corneal Endothelial Cells to Increased Intraocular Pressure

A Specular Microscopic Study

by

Kirsi Setälä

SCRIPTOR COPENHAGEN 1980

FROM THE DEPARTMENT OF OPHTHALMOLOGY UNIVERSITY
OF HELSINKI
(HEAD PROFESSOR SALME VANNAS M D)
HELSINKI FINLAND

RESPONSE OF HUMAN CORNEAL ENDOTHELIAL CELLS TO INCREASED INTRAOCULAR PRESSURE
— A specular microscopic study

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DOCTORAL THESIS

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These papers will be referred to in the text by the Roman numerals I—V

The transparency of the cornea depends upon its deturgescence which is regulated by the endothelial cells These cells are of crucial importance for the functioning of the cornea Several eye diseases primarily affect the endothelium (e g Fuchs dystrophy) leading to loss of corneal transparency and the need for corneal transplantation later in life

In the last few years the endothelial specular microscope has gained increasing importance (Maurice 1968 Laing et al 1975 Bourne & Kaufman 1976 a) This instrument permits direct observation of the intact eyeball for evaluating the morphology and density of the corneal endothelial cells in vivo Consequently pathological conditions in the endothelium can be detected at an earlier stage and the future transparency of the cornea can be predicted Between individuals there are great differences in the endothelial cell densities of the corneas but in each individual the endothelial cell densities of the two eyes are of the same order (Laule et al 1978 Sawa and Tanishima 1979 Olsen 1979) Consequently in uniocular eye diseases the contralateral healthy eyes afford a valid control series

So far no clinical studies have investigated the effect of increased intraocular pressure on the human corneal endothelium in vivo The purpose of this study was to examine whether increased intraocular pressure has any effect on endothelial cell density Cell counts were made with the specular microscope in patients with various types of unilaterally increased intraocular pressure chronic open angle capsular glaucoma acute angle closure glaucoma and the glaucomatocyclitic crisis Similar counts were made in patients with unilateral iridocyclitis but without increased intraocular pressure to show whether inflammation as such led to a decrease in endothelial cell density Changes in the endothelial cells were studied in patients with essential iris atrophy

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INTRODUCTION

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Anatomy and physiology of the cornea

The cornea is an avascular tissue occupying the front area of the eyeball Light reaches the retina through this transparent, refractive tissue which serves as a barrier between the air and the fluid in the anterior chamber The cornea consists of six layers epithelium, basement membrane, Bowman's layer, stroma Descemet s membrane, and endothelium Descemet's membrane is restricted to the posterior surface of the stroma and is considered to be the product of secretion by the endothelial cells It is secreted continuously throughout life (Hogan et al 1971, Collier 1975)
The endothelium is a single layer of hexagonal cells of mesodermal origin These cells contain the usual cellular organelles rough surfaced endoplasmic reticulum, ribosomes, Golgi apparatus and centrioles They also have unusually long mitochondria, which contain oxidative enzymes The organelles of the endothelial cells are characteristic of cells engaged in active transport and in synthesis of protein for secretion (Hogan et al 1971) Each cornea has about 300 000—500 000 endothelial cells covering an area of about 100 mm² (Svedbergh & Bill, 1972)
Human corneal endothelial cells do not regenerate, and the number of endothelial cells decreases with age (Kaufman et al 1966 Capella 1971, Laing et al 1975 1976, Bourne & Kaufman 1976 a Kaufman & Katz 1977)

Significance of the corneal endothelium

The endothelial cells act as pumps maintaining the cornea in a deturgescent state — *a state essential for corneal transparency* The adult human endothelium is a finite pool of cells in which mitotic division does not normally occur A single mitosis has been observed in an eyebank eye (Kaufman et al 1966) When endothelial cells are destroyed those that remain enlarge and spread or slide until the posterior corneal surface is again covered by a complete cellular monolayer (Doughman et al 1976) This ability to reestablish morphological continuity has been called the spreading potential or healing reserve (Bron & Brown 1974 Bourne et al 1976 Laing et al 1976 Shaw et al 1978)
In old people the endothelial cells are fewer and larger than in younger subjects and cell death due to normal ageing processes may be considered inevitable (Laing et al 1976 Bourne & Kaufman 1976 a) The endothelial cell density may also decrease as a result of acute or chronic damage Endo

thelial cell loss occurs in various eye operations such as corneal transplantation (Bourne & Kaufman 1976 b c Laing et al 1976 Forstot et al 1977) The minimal cell density that can keep the cornea clear and transparent cannot be determined because it also depends on the efficiency of the pumping mechanism of the cells The cornea may be thin and clear even with an endothelial cell density of less than 500 cells/mm² (Bourne & Kaufman 1976 c) However there must be a limit beyond which it is not possible for the remaining cells to cover the posterior corneal surface and function efficiently enough The cornea will then become cloudy (Shaw et al 1978) Before the specular microscope was available corneal endothelial cell function or insufficiency was assessed by measuring corneal thickness the thicker the stroma the less functionally sufficient the endothelium Specular microscopy has demonstrated that low endothelial cell densities are responsible for the local or diffuse postoperative oedema of the stroma (Bron & Brown 1974)

If the cornea has been damaged and the cell density has decreased the cell loss that occurs with age may lead to decompensation and corneal oedema many years after the original trauma Spencer et al (1966) described such delayed clouding in patients with congenital glaucoma The intraocular pressure in these patients had been well controlled and the corneas were clear 20 years after the glaucoma episode and surgery But when another 20 years had elapsed the corneas became oedematous because with normal losses due to age the reduced endothelial cell population could finally no longer maintain deturgescence

Examination of the corneal endothelium

Until recently the endothelium was examined with a slit lamp and only advanced pathological conditions could be detected The only means for assessing the viability of the endothelial cells was measurement of corneal thickness However corneal thickness depends on intraocular pressure tear flow and tear evaporation as well as on endothelial cell function Staining of corneal tissue has also been used to assess tissue viability With each of these methods we can detect current pathological conditions but cannot assess prospects for future corneal health

With the specular microscope invented by Maurice (1968) it was possible to investigate and photograph the endothelial cells of enucleated eyes Laing et al (1975) made improvements in the instrument and were able to photograph endothelial cells in vivo and Bourne & Kaufman (1976 a) developed the apparatus still further and made specular microscopy a routine examination The specular microscope enables us not only to detect pathological conditions at an earlier stage but also to predict the future health of the endothelium by directly observing the number of endothelial cells in the intact eyeball and their morphology Vogt (1920) described the technique for visualizing the endothelium with the slit lamp This non-contact technique has been reintroduced into clinical practice combined with photography (Brown 1970 Bron & Brown 1974 Holm 1978)

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Effect of age on the corneal endothelial cells

In the newborn the endothelial cells are small and compact, the nucleus occupying most of the cell and the cytoplasm being scanty The diameter of the cornea increases up to the age of 30 years, the cells enlarging but re maining regular and hexagonal Until middle age the cells can still enlarge if need be to cover a greater area and compensate for the normal cell death that occurs with age (Kaufman et al 1966, Hogan et al 1971, Capella 1971, Svedbergh & Bill 1972)

Irvine & Irvine (1953) observed no significant effect of age on the number of endothelial cells However, 80% of the eyes used in their study were from patients over 50 years old, and none were from patients under 25 The eyes were enucleated at autopsy and fixed in formalin, and the nuclei were stained for counting The mean number of nuclei per unit area was the same at different ages

Kaufman et al (1966) examined enucleated eyes in which the endothelium was stained with NADH diaphorase, and found that endothelial cell density decreased with age and pleomorphism increased

Capella (1971) reported that endothelial cells remained essentially un changed from the age of 15 to 50 years but at about 60—65 their size began to increase and pleomorphism also increased

Bourne & Kaufman (1976 a) used the contact specular microscope to examine patients of ages ranging from 7 to 85 years and found that cell density decreased by about 30% between the ages of 20 and 80 (from 3250 cells/mm² to 2250 cells/mm²) The corneal thickness did not correlate with the cell counts

Laing et al (1976) found that the area of the cells increases with age the mean cell area approximately doubling from age 20 to 80 They also noticed that cell area increases continuously and not suddenly at the age of 60—65

Endothelial cell density in different parts of the cornea

The area most often photographed with the specular microscope is the cent ral cornea this being technically the easiest to photograph

Irvine (1956) observed that the endothelial cell density was about 16% lower in the central part of the cornea than in the periphery He counted the nuclei of the endothelial cells in flat corneal sections from enucleated eyes However we cannot ignore the possibility of changes after death and of artefacts from the various procedures used

Blackwell et al (1977) photographed different areas of the cornea, the cent ral superior temporal and inferior in four groups of patients In normal young adults normal older adults and post-cataract adults they found no significant differences in cell numbers in the different areas Only in the intraocular lens group did the superior portion have fewer cells than the inferior However the number of cells in the central area was a useful measure since it was approximately an average of these numbers

Sturrock et al (1978) observed that the cell density in the central part of the

cornea was only about 3.2% lower than in the periphery (nasal and temporal part). They concluded that photographs and counts of the endothelial cells in the central part gave a good indication of the whole endothelial cell population in the normal cornea. However, they thought that after trauma such as a cataract operation the endothelial cell population must be unevenly distributed and that photography of the central cornea alone would not give a reliable result for the endothelial cell population as a whole.
Hoffer (1979) showed that in normal patients who have had no eye operations the endothelial cell density is the same in the superior, middle and inferior parts of the cornea. After operations for cataract, however, he found a great difference. The incision is made in the superior part of the cornea and the postoperative endothelial cell density is much lower in the superior part of the cornea than in the other parts. This difference in cell density persists for at least 9 years after the operation. Hoffer supposes that once the damaged area of the cornea has been covered with endothelial cells, the stimulus to further spreading of cells disappears and the differences remain constant.

Endothelial cell density in the right and left eyes

Kaufman et al. (1966) showed that 98% of the normal population had the same endothelial cell density in both eyes.
Laing et al. (1976) examined the area of the endothelial cells and found a small but statistically significant difference between the right and left eyes.
According to Sturrock et al. (1978), however, although there is great variation between the endothelial cell densities in persons of the same age, the difference in endothelial cell density between the right and left eyes of a normal healthy person is very small.
Laule et al. (1978) also found that in normal subjects a study of the endothelial cell population of one eye allows accurate prediction of the endothelial cell density in the fellow eye.

Effect of increased intraocular pressure on the corneal endothelial cells

Experimental studies

As early as 1873 Leber discovered localized endothelial defects corresponding to patches of corneal opacity in rabbits exposed to 110 mmHg (duration not stated).
No change from the normal appearance was observed in transmission electron microscopy when the IOP was raised (duration not stated) to 60—80 mmHg in vitro (Kaye et al. 1973).
Svedbergh (1975) studied the effects of a moderate rise (33—44 mmHg) in intraocular pressure lasting 3—7 h on the ultrastructure of the corneal endothelium in 10 adult vervet monkeys. The cells were often flattened and the unevenness of the cell surface was increased towards the anterior chamber. Pycnosis, exkaryocytosis and even loss of whole endothelial cells were visible as well.

Effect of age on the corneal endothelial cells

In the newborn the endothelial cells are small and compact the nucleus occupying most of the cell and the cytoplasm being scanty The diameter of the cornea increases up to the age of 30 years, the cells enlarging but re maining regular and hexagonal Until middle age the cells can still enlarge, if need be, to cover a greater area and compensate for the normal cell death that occurs with age (Kaufman et al 1966 Hogan et al 1971, Capella 1971 Svedbergh & Bill 1972)

Irvine & Irvine (1953) observed no significant effect of age on the number of endothelial cells However 80% of the eyes used in their study were from patients over 50 years old, and none were from patients under 25 The eyes were enucleated at autopsy and fixed in formalin, and the nuclei were stained for counting The mean number of nuclei per unit area was the same at different ages

Kaufman et al (1966) examined enucleated eyes in which the endothelium was stained with NADH diaphorase, and found that endothelial cell density decreased with age and pleomorphism increased

Capella (1971) reported that endothelial cells remained essentially un changed from the age of 15 to 50 years but at about 60—65 their size began to increase and pleomorphism also increased

Bourne & Kaufman (1976 a) used the contact specular microscope to examine patients of ages ranging from 7 to 85 years and found that cell density decreased by about 30% between the ages of 20 and 80 (from 3250 cells/mm² to 2250 cells/mm²) The corneal thickness did not correlate with the cell counts

Laing et al (1976) found that the area of the cells increases with age, the mean cell area approximately doubling from age 20 to 80 They also noticed that cell area increases continuously and not suddenly at the age of 60—65

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Effect of increased intraocular pressure on the corneal endothelial cells in man

During an attack of acute glaucoma the cornea swells Decompensation of the corneal endothelium permits excess fluid to enter the corneal stroma from the anterior chamber In acute glaucoma fluid may be forced into the stroma in spite of a healthy normal functioning endothelial layer Apparently, if the pressure attack lasts a certain time the endothelial cell layer becomes damaged and partly permeable to fluid (Stocker 1971)
Irvine (1956) studied 47 enucleated glaucomatous eyes in flat preparations He described flattening and attenuation of the endothelial cells The number of cells per unit area was usually decreased and in some cases the endothelium was totally absent No study has been published hitherto in which the endothelial cells in glaucomatous eyes were examined by specular microscopy

Effect of iridocyclitis on the corneal endothelial cells

In a patient who had had several severe attacks of iridocyclitis Stocker (1971) noticed oedema of the epithelium and cloudiness of the stroma in the areas that had no keratic precipitates (KPs) Nor was there oedema in the inferior area of the cornea where most of the KPs are situated Stocker supposed that the endothelial cells were damaged by the inflammatory process itself
In cases of iridocyclitis Honegger (1966) discovered thinning of the endothelium which did not correspond to fibrin or cellular deposits He assumed that this depended on some toxic effect
O'Connor (1972), however showed that in long standing uveitis oedema of the epithelium often appeared in the areas which corresponded exactly to the inflammatory keratic precipitates (KPs)
Inomata and Smelser (1970) induced uveitis in albino rabbits by intravitreal injection of serum albumin The inflammatory process caused oedema and cloudiness in the cornea The changes in the endothelium included vacuolization and infiltration by monocytes Many inflammatory cells lay between the endothelium and Descemet's membrane but there were very few changes in the cytoplasm of the endothelial cells These workers think it noteworthy that the inflammatory cells could pass between the endothelial cells and Descemet s membrane Most of the endothelial changes were observed under the precipitates There was no mention of intraocular pressure

Corneal endothelial cells in essential iris atrophy

Essential atrophy of the iris (EIA) is a rare usually unilateral disease of unknown aetiology characterized by secondary glaucoma slowly progressive atrophic changes in the iris, and changes in the chamber angle (Duke Elder 1966) Recently the hypothesis has been advanced that in essential iris atrophy important causal roles are played by degeneration of the corneal endothelium and growth and contraction of an ectopic endothelial membrane

(Yanoff & Fine 1975 Scheie et al 1976 Rodrigues et al 1978) Campbell et al (1978) have proposed a new designation for the syndrome primary proliferative endothelial degeneration The ectopic endothelial membrane has been detected in eyes that were enucleated because of far advanced changes due to secondary glaucoma and in trabeculectomy and iridectomy specimens In these previous studies the angle and trabeculum have been examined but not the endothelial cells of the central cornea *in vivo*

The present investigation was undertaken to determine whether increased intraocular pressure affects the cell density of the human corneal endothelium The effect of an inflammatory process was studied in patients with unilateral iridocyclitis but without elevated intraocular pressure The specular microscope was also used to evaluate corneal endothelial cell morphology in patients with essential iris atrophy
Comparisons were made in patients with the following diseases the healthy fellow eye being used as a control —

I Chronic capsular glaucoma,
II Glaucomatocyclitic crisis (Posner Schlossman syndrome)
III *Unilateral iritis, to ascertain whether an inflammatory process* affects endothelial cell density,
IV Acute angle closure glaucoma
V Essential iris atrophy, to find out whether specular microscopy can be used for diagnosing the disease

The present series consisted of five groups (table I) The patients were examined at the Eye Clinic University of Helsinki The study was performed during 1976—79

TABLE I PATIENTS OF THE PRESENT STUDY

Number of paper	Diagnosis	Number of patients	Sex F/M
I	Capsular glaucoma	27	20/7
II	Glaucomatocyclitic crisis	21	10/11
III	Iridocyclitis	60	32/28
IV	Acute angle-closure glaucoma	25	19/6
V	Essential iris atrophy iridoschisis and 2 undefined disorders of the iris	6	6/0
Total		139	87/52

I Patients with capsular glaucoma

There were 27 patients with uniocular capsular glaucoma (paper I) Age and sex distribution are seen in fig 1 (paper I) There were 20 women and seven men The majority of the patients (70%) were 65 years or older 16 (59%) being 65—75 years old The ocular tension at the time of photography and before treatment is seen in table II Treatment was started at the time of diagnosis but two patients (Nos 6 and 12) had no treatment at the time of photography As treatment pilocarpine was started routinely In addition nine patients had adrenalin The exact duration of the adrenalin treatment could not be calculated because some patients had already received this drug before being remitted to Helsinki University Eye Clinic No eye operations were performed in these patients

The follow up time of the patients varied from 1 month to 6 years This is because in patients with capsular glaucoma control of ocular tension is often

TABLE II Details of the patients with capsular glaucoma

Patient No	Age (years)	Sex	Time from diagnosis (months)	Duration of treatment (months)	Adrenalin treatment	Exfoliation in fellow eye	Pressure (mmHg) in the affected eye		Field defect in affected eye
							Before treatment	At time of photography	
1	70	F	18	18	+	+	34	18	+
2	59	F	12	12	—	—	28	20	+
3	65	F	12	12	—	—	32	23	—
4	70	M	6	6	+	—	51	16	+
5	75	M	4	4	—	—	28	21	—
6	73	F	5	—	—	—	29	29	—
7	60	F	12	12	+	—	40	35	—
8	59	F	36	36	+	—	48	40	+
9	61	F	2	2	—	+	40	18	—
10	82	F	12	12	+	+	52	30	+
11	72	F	72	72	—	—	33	17	+
12	63	M	3	—	—	—	36	36	—
13	63	M	24	24	—	—	35	30	—
14	74	F	24	24	+	+	34	20	—
15	71	F	5	5	+	+	40	24	—
16	81	F	1	1	—	—	40	40	+
17	80	F	12	12	—	—	28	17	+
18	68	M	60	60	+	—	38	19	+
19	70	F	3	3	—	+	28	18	—
20	69	F	36	36	—	—	30	25	—
21	69	F	24	24	—	+	28	18	—
22	69	F	12	12	+	—	28	16	—
23	69	F	10	10	—	—	34	22	—
24	68	F	1	1	—	—	50	27	—
25	67	M	1	1	—	—	40	22	—
26	62	F	3	3	—	—	54	28	+
27	61	M	4	4	—	—	30	22	+

difficult without glaucoma operations Half of the patients (14) were photographed 1 year or more after diagnosis and only four patients 3 or more years after diagnosis
Eleven of the 27 patients had visual field defects (table II and paper I table I and fig 2)

II Patients with the glaucomatocyclitic crisis (Posner-Schlossman syndrome)

There were 21 patients with Posner Schlossman syndrome Their ages ranged from 23 to 67 years Three patients had their first attack between 30 and 40 years but usually the disease began before the age of 30 (paper II table I) Ten of the patients were women and 11 were men
Seven patients had fewer than five attacks and the remainder (14) had had more than five — usually more than ten attacks Some patients had had dozens of attacks The ocular tensions measured during attacks are seen in paper II table I

III Patients with iridocyclitis

The series comprised 60 patients 32 women and 28 men Their ages ranged from 11 to 74 years with a mean of 41 4 years Age and sex distributions are seen in paper III fig 1 Every patient had unilateral iridocyclitis the contralateral eye being externally and internally normal, and there was no history of inflammation The series was selected so that both eyes had normal intraocular pressure (10—20 mm Hg) In most cases (45) the aetiology of the disease remained obscure as is usual with iridocyclitis In six cases the underlying disease was ankylosing spondylitis in six cases rheumatoid arthritis and in two cases sarcoidosis One patient had Reiter s syndrome (paper III table I) The patients were divided into three groups according to their signs and symptoms (Hogan et al 1959) The first group comprised seven patients with severe chronic iridocyclitis with large mutton fat keratic precipitates (KP s) The two patients with sarcoidosis belonged to this group In two patients the iridocyclitis had begun 1—2 years before the photography and they had had a few short periods without inflammation
The second group comprised 35 patients some of them had had several attacks and seven patients had had more than ten attacks However another seven patients had had only one attack and no recurrences before the specular photography The frequency of iridocyclitic attacks in the other patients of this group ranged from two to ten attacks The feature common to all these patients is that every one had small or medium sized round white KPs
The third group comprised patients with mild iritis in whom no KPs were discovered during examinations One patient in this group had had more than ten attacks but ten patients had had no recurrences and the rest had had two to four attacks
Of the 60 patients with iridocyclitis 17 had had only one attack of 1—3 weeks duration These patients were photographed at the end of the attack

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Ophthalmological examination

The ophthalmological examination included a test of visual acuity slit lamp examination measurement of intraocular pressure tonography analysis of visual fields and inspection of the ocular fundus The visual fields were investigated with a Goldmann kinetic perimeter and a Friedmann visual field analyzer Gonioscopy was performed with a Goldmann lens Tonography was performed as described by Garner (1965)

Photomicrography of the corneal endothelium

The contact specular microscope

The contact specular microscope (Seyber Inc) used in Helsinki University Eye Clinic is seen in use in the photograph (fig 1) The patient s head rests on the head stage The objective lens is a x 20 water immersion lens with a



Fig 1 Contact specular microscope in use Patient on left

Twenty nine patients had had two or more iridocyclitic attacks before photography Only four of these patients had a history of less than 2 years of iritis, and in the remaining 25 patients 2 or more years had elapsed between the first attack and the time of photography Fourteen patients had a chronic disease or several recurrences with only short healthy intervals

IV Patients with acute angle-closure glaucoma

The series consisted of 25 patients, 19 women and 6 men Their mean age was 66 3 years All but one of the patients was examined soon after the first acute attack Patient No 8 had suffered from an attack of acute glaucoma of 2 days' duration in the same eye 20 years earlier (paper IV, table I) All the fellow eyes had normal ocular pressure values and no symptoms such as blurring of vision or ocular pain In five of these patients the ocular pain, blurring of vision, vomiting and nausea had lasted 3 days or longer In the others the history was shorter Intraocular pressure on admission is seen in paper IV, table I The endothelial specular photomicrographs were taken when the intraocular pressure had been lowered with intravenous (acetazolamide or mannitol) or local (pilocarpine) therapy Visualization of the endothelial cells is not possible when the pressure is high and the cornea hazy

Peripheral iridectomy was performed within 4—6 days of the pressure attack Where the angle was narrow, prophylactic surgery was also performed on the normotensive fellow eye Trabeculectomy was performed on the affected eye in only two of the patients Whenever possible, the endothelial cells were also photographed 6—24 months postoperatively

V Patients with essential iris atrophy

We had three patients with typical essential iris atrophy (paper V, table I) All were women The first patient was 35 years old and the duration of her disease was 6 years She had always had normal ocular pressures in both eyes In her left eye she had typical essential iris atrophy (paper V fig 1) The second and third patients were 42 and 63 years old the duration of their disease being 25 and 7 years respectively In both these patients the intraocular pressure in the affected eye was increased, but in the second (No 2) patient this had been normalized with local therapy In the third patient the intraocular pressure was somewhat elevated in spite of therapy As a control one patient with iridoschisis (paper V No 4) and two patients with pupillary malformation (paper V Nos 5 and 6) were also photographed with the contact specular microscope

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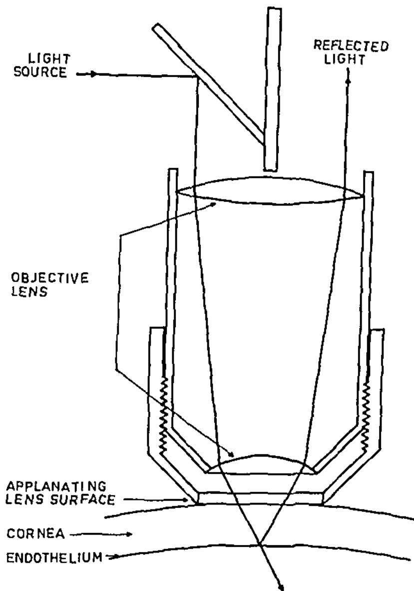


Fig 2 Diagram showing incident and reflected light in the contact specular microscope

dipping cone The objective lens is used both for illumination and for viewing (fig 2) The dipping cone of the objective lens flattens the corneal surface The close up picture shows how the applanating lens touches the patient's corneal (fig 3)

A flashlight of short duration is needed to eliminate disturbances due to rapid ocular movements during photography The endothelial picture is focused by changing the distance of the dipping cone lens from the objective lens (fig 2)

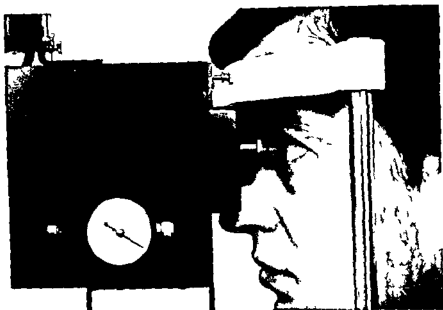


Fig 3 Close up photograph of the conical lens of the specular microscope touching the cornea

A narrow light beam is projected onto the posterior corneal surface at a near normal angle of incidence Most of the light is transmitted into the aqueous humour A small fraction 0 02% of the light is reflected back from the aqueous humour-endothelial cell interface The reflected light is collected by the objective lens of the photomicroscope and forms an image of the corneal endothelium on the camera film plate A small proportion of light is also reflected on the film from other corneal interfaces If the slit is wide more light is reflected from the epithelium and the anterior parts of the cornea and this means poor contrast i e endothelial cell outlines are ill-defined But a narrow slit although it illuminates fewer cells gives good contrast and definition of cell outlines

Examination with the contact specular microscope

Examination of the endothelium with the specular microscope is a safe procedure Corneal surface anaesthesia is necessary The patient should be requested to hold the head and eye steady for sharp pictures
Contact with the dipping cone of the microscope occasionally causes some minute localized opacities in the epithelium in the same way as in applanation tonometry These changes disappear within a few hours Sharp pictures can be taken with the specular microscope only if the cornea is relatively clear The technique has been used even on the first postoperative day after cataract extraction without any damage to the eye (Bourne 1976) Any part of the corneal endothelium can be photographed but most publications have concentrated on the central part

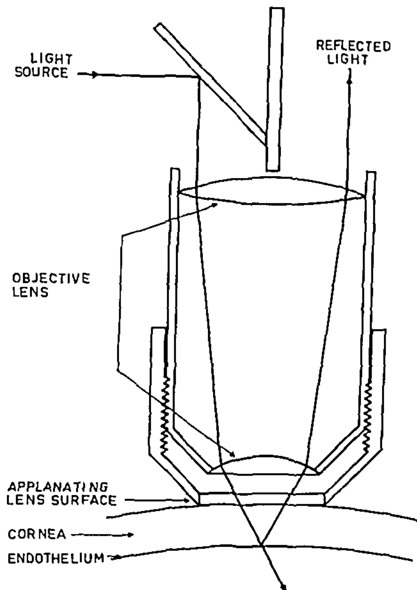


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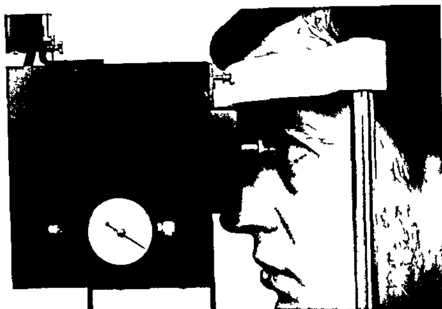


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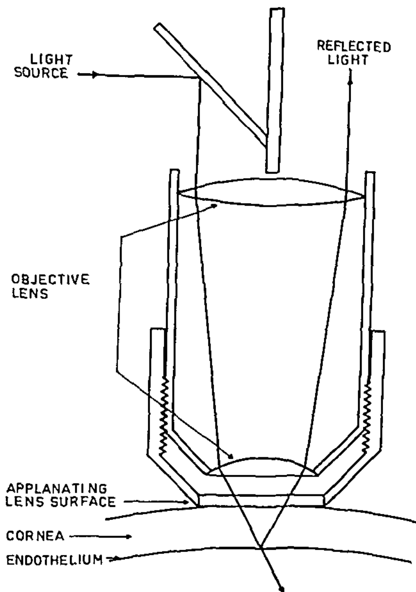


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were excluded by marking every cell counted The endothelial cells cut by two adjacent sides of the rectangle were included in the count but those cutting the opposite sides were excluded (fig 4) As the square magnification was 728^2 the area counted corresponded to a natural size of 0 012 mm² so the cell count divided by 0 012 gave the cell density per mm²

Reliability of the cell counts

In order to evaluate the cell counting technique and to ascertain the inter observer error of the counting procedure the second count was made by myself from the patients with acute glaucoma This series included 25 patients and counting was done blindly as in paper IV without knowledge of the patient or of whether the photograph was of the affected or the healthy eye

The results of this second count are given in Table III They show differences in the same direction as in paper IV The mean difference between the glaucomatous and control eyes is 10 4% (in paper IV it was 9 7%)

In order to investigate the reliability of the counting method and of the differences found between the affected and healthy eyes let us formulate a hypothesis

The O hypothesis The difference between the counts from the two eyes of the same person is due to the inaccuracy of the observations and so equals the difference between two counts from the same eye

To test the O hypothesis we shall compute the following two variance estimates

I The variance estimate of the observations between the two counts from the same eye (made by two different observers)

$$S_1^2 = \frac{1}{2N} \cdot \sum_{V=1}^{N} \Delta_V^2 = 5597$$

II The variance estimate between the counts from the affected eye and the fellow eye (counts made by the same person)

$$S_2^2 = \frac{1}{2N} \cdot \sum_{V=1}^{N} \Delta_v^2 = 110292$$

Technique of photography

Both eyes of all patients were photographed with the clinical specular mic roscope (Seyber Inc) High speed (Kodak Tri x) film was used routinely Photography was performed under controlled standard conditions The patients were given a fixation target to make sure that the central corneal endothelium was photographed in each case fixation was also checked by the investigator Ten to fifteen photographs were taken of each eye in some cases more photographs had to be taken because of poor visualization of the endothelial cells Five of the pictures with the best contrast were then selected for determination of endothelial cell density, in a few cases we had to be content with only three clear pictures The magnification of the specu lar microscope was calculated by photographing the surface of a glass slide on which calibration lines were etched at 10 μ intervals The photograph was taken through an aqueous medium with the dipping cone at the same distance from the objective lens as it would be when a cornea of normal thickness is photographed This calibrated picture was then magnified exactly x 500 and the magnification of the specular microscope was found to be x 100

Endothelial cells of patients with essential iris atrophy were also photo graphed with a non-contact specular microscope constructed by A Vannas at Helsinki University Eye Clinic (paper V)



Fig 4

Photomicrograph of human corneal endothelium with a 0 012 mm rectangle The cell density/ mm is counted from the cells inside the rectangle and those cutting two adjacent borders

Evaluation of the photographs

The endothelial cell count was done by projecting the negative which had a linear magnification of x 100 onto a screen at a linear magnification of x 7 28 Counting was done in the same way in all cases without knowledge of whether the right or left eye was affected In papers III and IV the count ing was done by another experienced observer and in the other papers by myself The cells in an area of 40 x 160 mm^2 were counted by placing a rectangle of transparent paper of this size on the screen and counting errors

were excluded by marking every cell counted The endothelial cells cut by two adjacent sides of the rectangle were included in the count but those cutting the opposite sides were excluded (fig 4) As the square magnification was 728[2] the area counted corresponded to a natural size of 0 012 mm[2] so the cell count divided by 0 012 gave the cell density per mm[2]

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Starting from these two variance estimates we now proceed to make the F test

$$F\,(n,n) = \frac{S_2^2}{S_1^2} = 19\ 7$$

The result clearly shows that we can reject the O hypothesis with a certainty of 0 999 (= 1 0 001) and state that

S_2^2 is very significantly larger than S_1^2

TABLE III
Control counts of corneal endothelial cells in patients with acute glaucoma

Case No	Endothelial cell densities: affected eye (cells/mm²)	fellow eye (cells/mm²)	difference (%)
1	662	1656	60 0
2	662	2070	68 0
3	766	1904	59 8
4	1490	2484	40 0
5	2318	2815	17 7
6	2070	2236	7 4
7	2070	2152	3 8
8	2070	2152	3 8
9	2318	2401	3 5
10	2815	2898	2 9
11	1904	1987	4 2
12	2815	3064	8 1
13	2567	2567	0
14	2650	2650	0
15	2236	2318	3 5
16	2484	2567	3 2
17	2815	2732	—3 0
18	2484	2650	6 3
19	2650	2484	—6 7
20	1904	1987	4 2
21	2153	2153	0
22	2153	2318	7 1
23	2567	2650	3 1
24	2236	2236	0
25	2567	2484	—3 3
Mean	2137	2384	10 4

This result leads us to the conclusion that the variance between the two eyes of the same patient greatly exceeds the variance due to the inaccuracy of the observations

The numerically equal results for pairs of eyes in papers I—IV (and Table III) are explained by the small field (= 0 012 mm²) counted Because of this it was not possible to calculate the absolute differences between densities

For evaluation of the results statistical expertise was gained from Mr Erkki Järvinen M S of the Institute for Occupational Health

Changes in magnification

Changes in corneal thickness can affect the magnification on the film plate However within the range normally seen (0 5—0 7 mm) the error is less than 1 % (Bourne & Enoch 1976)

1 Endothelial cell density in capsular glaucoma

Of the 27 patients 15 had a lower endothelial cell density in the glaucomatous eye than in the healthy fellow eye used as a control Another 10 patients had the same cell density in the affected and healthy eyes Two patients had a lower cell density in the normotensive eye than in the glaucomatous eye (paper I table I) Although the series is small, these densities confirm with statistical significance the direction of the difference (2P < 0 01, sign test) The greatest difference between an affected eye and its fellow was 14% (paper I table I) The mean endothelial cell count in the affected eyes was 2386 cells/mm² and in the healthy eyes 2516 cells/mm² The difference is 5%

Seven patients had exfoliated material in the normotensive contralateral eye as well (paper I, table I) The glaucomatous eyes of these patients showed a cell density of 2364 cells/mm² and the control eyes of 2474 cells/mm² The difference was 4%

In two patients glaucoma therapy had not been started before endothelial photography The mean endothelial cell density in the affected eyes was 2319 cells/mm² and in the control eyes 2464 cells/mm² The difference was 5% (paper I table I)

On comparison of the 15 cases which showed a reduced endothelial cell density with the 12 cases in which this change was not observed no correlation was found with the following variables

- Intraocular pressure on admission or pressure difference between the affected and control eyes
- Variations in the diurnal curve of IOP
- The C value or Po/C ratio
- Duration of glaucoma after diagnosis although the pressures were highly resistant to medical treatment Seven patients had been under observation for 2 years or longer after the diagnosis The mean difference in endothelial cell density between the eyes of these patients was 2 5%
- Visual field defect The mean endothelial cell difference in patients with a field defect in the glaucomatous eye was 4%

Comment In unilateral capsular glaucoma corneal endothelial cell density was lower in 15 glaucomatous eyes and only in two healthy eyes which provides statistically significant confirmation of the direction of the difference

II Endothelial cell density in the glaucomatocyclitic crisis (Posner Schlossman syndrome)

Of the 21 patients 16 had a lower endothelial cell density in the affected eye than in the healthy contralateral eye Five patients had the same cell density in both eyes and not a single patient had a higher cell density in the affected eye than in its fellow (paper II table I) The lower cell density in the 16 affected eyes gives a statistical significance for the direction of the difference ($2P < 0.001$) The mean endothelial cell count in the affected eyes was 2476 cells/mm^2 and in the healthy eyes 2821 cells/mm^2 The dif ference is 12% The greatest difference in endothelial cell density between an affected eye and its fellow was 27% (paper II table I and fig 1)
When the difference in endothelial cell count between the healthy and af fected eye was more than 20% the disease had lasted for several years with several pressure attacks (paper II fig 1) In five patients the two eyes had equal cell densities Four of these patients had had only one attack but the fifth had had two attacks
Comment Posner Schlossman attacks reduce the endothelial cell density the loss of endothelial cells correlating with the number of Posner Schloss man attacks

III Endothelial cell density in iridocyclitis

The patients with iridocyclitis were classified into three subgroups
The first subgroup of seven patients was characterized by severe iridocyclitis with large irregular fatty keratic precipitates Five patients in this subgroup showed a distinctly lower endothelial cell density in the affected eye (paper III table 2 A)
In the second subgroup the disease was characterized by small round white precipitates This subgroup comprised 35 patients Cell density was lower in the affected eye in 13 patients but equal in 16 Six patients had a slightly higher endothelial cell count in the iritic eye The mean difference between the affected eyes and the healthy eyes was 0 7% this difference not being statistically significant (paper III table 2 B)
In the third subgroup 18 patients displayed an aqueous flare and cells in the anterior chamber but no precipitates on the corneal *endothelium Only* four of these patients had a lower cell density in the affected eye whereas ten patients had the same cell density in both eyes and four patients had a lower cell density in the healthy eye (paper III table 2 C)
Comment Chronic severe iridocyclitis with mutton fat KPs was associated with a reduced central endothelial cell *count Neither the* inflammatory process itself nor the round white KPs seemed to have a deleterious *effect* on the endothelial cell density in the central cornea

IV Endothelial cell density in acute glaucoma

This group consisted of 25 patients In five patients *the acute* glaucoma attack had lasted from 3 days to 2 weeks The mean endothelial cell density

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DISCUSSION

The purpose of this study was to investigate whether increased intraocular pressure has any effect on the human corneal endothelial cell density For this purpose I chose different types of uniocular glaucoma this enabled me to eliminate other possibly detrimental factors that might reduce endothelial cell density For chronic open angle glaucoma it would have been logical to choose patients with glaucoma simplex In most cases however glau coma simplex is bilateral and because a healthy fellow eye was needed to provide a valid control series capsular glaucoma was chosen Capsular glaucoma is a chronic open angle glaucoma with pseudoexfoliation Acute angle-closure glaucoma occurs in eyes with an anatomically shallow anterior chamber The attack of acute glaucoma occurs when the angle is closed and aqueous humour cannot escape from the eye However high pressure persisting for several days may lead to alterations in the aqueous humour (for example the oxygen content decreases) and these changes may affect the endothelium augmenting the effect of the increased intraocular pressure itself The glaucomatocyclitic crisis (Posner Schlossman syndrome) is a kind of acute inflammation of the uveal tract dominated by signs of acute in creased intraocular pressure and the anterior chamber is of normal depth These three disease entities though all involving increased intraocular pres sure differ greatly from each other in all of them however the direction of the difference in endothelial cell density between the glaucomatous eye and the healthy fellow eye was the same So we can suppose that increased intraocular pressure leads to a reduction in corneal endothelial cell density

In all age groups endothelial cell density varies from individual to indivi dual Recent attempts to determine whether an operation or trauma has influenced endothelial cell density have therefore used the contralateral eye as a control Kaufman et al (1966) Laule et al (1978) Sturrock et al (1978) and recently Sawa & Tanishima (1979) have come to the *conclusion* that the endothelial cell density of the right and left eyes of healthy *persons* are the same Only Laing et al (1976) were unable to confirm the above re sult and they used a slightly different technique Their study *showed* a statistically significant 5% difference between the mean endothelial cell areas of the left and right eyes

The area *shown* in every photograph is small less than 0 05% of the total endothelial area However statistical *evaluations mady* by Sperling & Gundersen (1978) suggest that these numbers do give precise data Sturrock et al (1978) followed 16 eyes at 7 week intervals and concluded that endo

in these patients was 48% lower in the affected eye than in the normotensive fellow eye In the remaining patients the acute attack lasted less than 3 days and the endothelial cell density in the affected eye was slightly lower than or equal to that in the fellow eye There seemed to be a correlation between the number of endothelial cells lost and the duration of the glaucoma attack (paper IV fig 2) The intraocular pressure level did not seem to correlate with the endothelial cell loss (paper IV, fig 1)
The endothelial cell loss after iridectomy was 4 9% in the affected eyes and 4 6% in the healthy eyes that had had a prophylactic iridectomy (paper IV, table 2)
Comment High intraocular pressure lasting for 3 days or more lowered the central endothelial cell density by a mean of 48% A rise in pressure lasting from a few hours to 2 days had only a minimal effect if any, on the endothelial cell count In this group operative treatment caused an endothelial cell loss of about 4 8%

V Endothelial cells in essential iris atrophy

The specular microscope was used to study the corneal endothelium in three patients with essential iris atrophy and three patients with some other disorder of the iris It was hardly possible to make an accurate estimate of the endothelial cell density, however, typical features of the disease were pleomorphic and enlarged endothelial cells with abnormal cell structure Two patients had elevated IOP and advanced changes in the iris The third patient had essential iris atrophy and normal intraocular pressure, however, in this patient the endothelial cells showed similar morphological changes In these three patients with essential iris atrophy the photomicrographs were opposite in appearance to those of normal endothelial cells dark areas were enclosed in bright boundaries The number of endothelial cells was decreased in the eyes with essential iris atrophy but the exact cell count could not be determined owing to haziness
In addition to the above mentioned patients with essential iris atrophy one patient with iridoschisis and two with undefined local iris atrophy were photographed for comparison High intraocular pressures that resisted drug therapy had been measured on several occasions in the affected eye of the patient with iridoschisis, and surgery was necessary The endothelial cell density was only 650 cells/mm² as compared with 3000 cells/mm² in the control eye The endothelial cell morphology in the affected eye was normal (hexagonal) and the cells were clearly visualized In the two patients with other iridal disorders the endothelial morphology was unremarkable (paper V table I)
Comment The specular microscope is a useful aid in differentiating essential iris atrophy from other disorders of the iris

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Topical medication (especially with solutions including preservatives) might affect the endothelial cell density but our findings do not support the idea that glaucoma medication leads to lowering of endothelial cell density Waltman et al (1977) noticed a significant reduction in the endothelial cell count in glaucomatous eyes treated with adrenalin as compared with their untreated fellow eyes however these workers did not take into account the effect of increased intraocular pressure In our series of patients with capsular glaucoma there was no correlation between endothelial cell loss and adrenalin treatment (table II and paper I table I) In patients with Posner Schlossman syndrome the loss of endothelial cells definitely de pended on pressure attacks most patients with this syndrome had received only acetazolamide as therapy for the attack and no topical medication Moreover if topical medication with preservatives had a marked effect on endothelial cell density then patients with iridocyclitis should show greater differences between the cell densities of the two eyes because even the groups with small or medium sized precipitates included patients who had received topical medication in liberal amounts cortisone drops (initially every hour) mydriatic drops (usually three times a day) for many weeks or even months

The decrease in endothelial cell density in patients with capsular glaucoma was not observed to correlate with the duration of treatment It is well known that capsular glaucoma may exist for many years especially if the condition is unilateral before a diagnosis is made With the chronically high IOP the cornea is clear and the patient usually has no symptoms until he notices decreased visual acuity or the high IOP is discovered at a routine eye examination Hence it is impossible to determine the duration of cap sular glaucoma One explanation for the lack of correlation between the endothelial cell density and the visual field defect might be that in some patients the endothelial cells are more resistant to increased pressure than in others

Acutely elevated intraocular pressure presumably leads to increased leakage through the intercellular spaces which up to a certain intraocular pressure level is counteracted by the posteriorly directed pump Increased cell com pression and distension of the whole bulb also occur the latter leading to lateral stretching of the endothelial cells (Kaye et al 1973) According to Svedbergh (1975) in acute glaucoma endothelial cell damage is marked and probably rapid whereas in chronic glaucoma the damage is more gradual Svedbergh observed flattening of the cells and even loss of whole endothelial cells which in other words means a decrease in cell density although there was only a moderate rise in intraocular pressure lasting about 3—7 hours In our patients however no clear difference was observed between the cell densities of the two eyes after an attack of acute glaucoma lasting from a few hours to 2 days We can speculate that perhaps the perfusion system which Svedbergh used in his experiments although it did not cause damage to the endothelial cells of the control eye (12—15 mmHg) made these cells more susceptible to the effects of even moderate and short term increases

thelial cell density was the same at successive photographings Although the endothelial cell number in each photograph is small (from 10 to 100) as compared with the total endothelial cell population of 300 000—500 000 cells the present technique is reliable This is also shown by the control count of patients with acute glaucoma It is difficult or impossible to know which area is represented in each photograph However continual ocular movement ensures that each picture is from a different area

One of the difficulties in specular photography is that many areas of the endothelium cannot be visualized clearly enough because of variability in the thickness of Descemet's membrane Blurred photographs which are impossible to analyze perhaps represent areas where the cells are diseased

Some recent studies (Shaw et al 1978, Sawa & Tanishima 1979) have used an automatic image analysis system that measures individual cells The results of these studies are in accord with those obtained by manual measurement of the cells in a given area (Shaw et al 1978) Manual methods are time-consuming and associated with human errors However, it is worth mentioning that in the automatic system variations in the level of shading across individual endothelial cells and the image field are not entirely eliminated and cell borders may not be uniformly sharp, so cell outlines are traced with ink on a sheet (Shaw et al 1978) and this may also introduce human error

Since the development of the specular microscope numerous studies have been made on how various traumas and operations affect the cells of the corneal endothelium However, there have been only a few studies on how various eye diseases affect the corneal endothelial cells

None of the earlier studies with the specular microscope have concerned the impact of increased intraocular pressure on endothelial cell density There is only Irvine s study of enucleated glaucomatous eyes (1956) in which he observed thinning of the endothelial cells and mentioned that the cell density was often reduced However, postmortem changes cannot be totally excluded

Our results show that increased intraocular pressure reduces endothelial cell density In the patients with chronic capsular glaucoma the differences in endothelial cell density between the affected and fellow eyes were not great, but the cell density was lower in 15 glaucomatous eyes and in only two healthy eyes which confirms the statistical significance of the direction of the difference If capsular glaucoma did not affect endothelial cell density, the ratio would not be so uneven

Besides intraocular pressure itself another factor that may have reduced endothelial cell density in the group of patients with capsular glaucoma is pseudoexfoliation It is noteworthy that in seven patients the control eye displayed exfoliation without elevated intraocular pressure In these patients the endothelial cell count was mostly lower in the affected eye which argues against the notion that exfoliation is responsible for reducing endothelial cell density The cell densities in these patients with pseudoexfoliation in both eyes correspond well to the densities in other subjects of the same age

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Besides intraocular pressure itself, another factor that may have reduced endothelial cell density in the group of patients with capsular glaucoma is pseudoexfoliation It is noteworthy that in seven patients the control eye displayed exfoliation without elevated intraocular pressure In these patients the endothelial cell count was mostly lower in the affected eye which argues against the notion that exfoliation is responsible for reducing endothelial cell density The cell densities in these patients with pseudoexfoliation in both eyes correspond well to the densities in other subjects of the same age

Topical medication (especially with solutions including preservatives) might affect the endothelial cell density but our findings do not support the idea that glaucoma medication leads to lowering of endothelial cell density Waltman et al (1977) noticed a significant reduction in the endothelial cell count in glaucomatous eyes treated with adrenalin as compared with their untreated fellow eyes however these workers did not take into account the effect of increased intraocular pressure In our series of patients with capsular glaucoma there was no correlation between endothelial cell loss and adrenalin treatment (table II and paper I table I) In patients with Posner Schlossman syndrome the loss of endothelial cells definitely de pended on pressure attacks most patients with this syndrome had received only acetazolamide as therapy for the attack and no topical medication Moreover if topical medication with preservatives had a marked effect on endothelial cell density then patients with iridocyclitis should show greater differences between the cell densities of the two eyes because even the groups with small or medium sized precipitates included patients who had received topical medication in liberal amounts cortisone drops (initially every hour) mydriatic drops (usually three times a day) for many weeks or even months

The decrease in endothelial cell density in patients with capsular glaucoma was not observed to correlate with the duration of treatment It is well known that capsular glaucoma may exist for many years especially if the condition is unilateral before a diagnosis is made With the chronically high IOP the cornea is clear and the patient usually has no symptoms until he notices decreased visual acuity or the high IOP is discovered at a routine eye examination Hence it is impossible to determine the duration of capsular glaucoma One explanation for the lack of correlation between the endothelial cell density and the visual field defect might be that in some patients the endothelial cells are more resistant to increased pressure than in others

Acutely elevated intraocular pressure presumably leads to increased leakage through the intercellular spaces which up to a certain intraocular pressure level is counteracted by the posteriorly directed pump Increased cell compression and distension of the whole bulb also occur the latter leading to lateral stretching of the endothelial cells (Kaye et al 1973) According to Svedbergh (1975) in acute glaucoma endothelial cell damage is marked and probably rapid whereas in chronic glaucoma the damage is more gradual Svedbergh observed flattening of the cells and even loss of whole endothelial cells which in other words means a decrease in cell density although there was only a moderate rise in intraocular pressure lasting about 3—7 hours In our patients however no clear difference was observed between the cell densities of the two eyes after an attack of acute glaucoma lasting from a few hours to 2 days We can speculate that perhaps the perfusion system which Svedbergh used in his experiments although it did not cause damage to the endothelial cells of the control eye (12—15 mmHg) made these cells more susceptible to the effects of even *moderate and* short term increases

thelial cell density was the same at successive photographings Although the endothelial cell number in each photograph is small (from 10 to 100) as compared with the total endothelial cell population of 300,000—500 000 cells, the present technique is reliable This is also shown by the control count of patients with acute glaucoma It is difficult or impossible to know which area is represented in each photograph However, continual ocular movement ensures that each picture is from a different area

One of the difficulties in specular photography is that many areas of the endothelium cannot be visualized clearly enough because of variability in the thickness of Descemet's membrane Blurred photographs which are impossible to analyze perhaps represent areas where the cells are diseased

Some recent studies (Shaw et al 1978 Sawa & Tanishima 1979) have used an automatic image analysis system that measures individual cells The results of these studies are in accord with those obtained by manual measurement of the cells in a given area (Shaw et al 1978) Manual methods are time-consuming and associated with human errors However, it is worth mentioning that in the automatic system variations in the level of shading across individual endothelial cells and the image field are not entirely eliminated and cell borders may not be uniformly sharp so cell outlines are traced with ink on a sheet (Shaw et al 1978), and this may also introduce human error

Since the development of the specular microscope numerous studies have been made on how various traumas and operations affect the cells of the corneal endothelium However, there have been only a few studies on how various eye diseases affect the corneal endothelial cells

None of the earlier studies with the specular microscope have concerned the impact of increased intraocular pressure on endothelial cell density There is only Irvine's study of enucleated glaucomatous eyes (1956) in which he observed thinning of the endothelial cells and mentioned that the cell density was often reduced However, postmortem changes cannot be totally excluded

Our results show that increased intraocular pressure reduces endothelial cell density In the patients with chronic capsular glaucoma the differences in endothelial cell density between the affected and fellow eyes were not great but the cell density was lower in 15 glaucomatous eyes and in only two healthy eyes which confirms the statistical significance of the direction of the difference If capsular glaucoma did not affect endothelial cell density the ratio would not be so uneven

Besides intraocular pressure itself, another factor that may have reduced endothelial cell density in the group of patients with capsular glaucoma is pseudoexfoliation It is noteworthy that in seven patients the control eye displayed exfoliation without elevated intraocular pressure In these patients the endothelial cell count was mostly lower in the affected eye which argues against the notion that exfoliation is responsible for reducing endothelial cell density The cell densities in these patients with pseudoexfoliation in both eyes correspond well to the densities in other subjects of the same age

The conclusion reached is that increased intraocular pressure leads to a reduction in corneal endothelial cell density This change is usually not crucial for corneal clarity but clear corneas with a low endothelial cell density are vulnerable to the effects of further trauma operation and time In corneal transplantation for example it is important to transplant as many endothelial cells as possible (Bigar et al 1976) It would be unjustified to transplant a cornea from an eye with absolute glaucoma even though the cornea might stay clear for some time after the operation The present results indicate that in eyes that have suffered from increased IOP the cornea may have reduced endothelial cell density being therefore probably more vulnerable to any intraocular surgery

in IOP, and, moreover, animal experiments cannot be assumed automatically to apply to human beings

Although attacks of acute glaucoma and of the Posner Schlossman syndrome differ in that in acute glaucoma the epithelium and stroma of the cornea are oedematous whereas in a Posner Schlossman attack the cornea is quite transparent, the results we obtained in these two groups of patients (papers II and IV) show a good correlation The effect of the duration (and number) of Posner Schlossman attacks could be clearly observed in patients with P S syndrome The endothelial cell densities might be used in patients with P S syndrome to evaluate whether they have had previous P S attacks without being aware of it

One might well ask what possible effect hypotonia ($T < 10$ mmHg) of the eye could exert on the endothelial cell densities In the seven eyes with chronic iridocyclitis the mean intraocular pressure of the diseased eyes was 12 mmHg and that of the control eyes 14 mmHg Because we had no group with ocular hypotonia we could not study the relation between endothelial cell density and depressed IOP Moreover, severe iridocyclitis with ocular hypotonia might have exerted so many other deleterious effects on the endothelial cells that the role of depressed IOP would have been impossible to separate To assess the possible impact of hypotonia one could photograph the endothelial cells of patients with retinal ablation, for example

Patients with iridocyclitis were examined especially for comparison with the patients with P S syndrome Patients with small round KPs which seem to be of the same kind as those occurring in the P S syndrome had approximately the same cell densities in the two eyes Neither the inflammatory process itself nor the small KPs had any effect on endothelial cell density, so it seems probable that the decreased endothelial cell density in patients with P S was due to the attacks of high pressure An interesting result in the iridocyclitic group is that in patients with mutton fat KPs and severe iridocyclitis 71 % of the affected eyes had a lower cell density than the healthy fellow eyes This is in good accord with O Connor's findings (1972) It seems logical to suppose that fatty KPs cause local damage to the endothelial cells

In patients with essential iris atrophy (EIA) the endothelial cells of the affected eyes seemed to be enlarged, being up to two to three times the normal size the cell borders were distorted, and the cells were irregularly polygonal instead of regularly hexagonal The corneas of our patients with EIA appeared quite normal in biomicroscopy only specular microscopy revealed the profound changes in the endothelial cells Hetherington (1978) has observed similar changes in patients with Chandler s syndrome This syndrome EIA and the iris naevus syndrome are considered to be variant clinical manifestations of a single disease entity that involves the corneal endothelium (Shields 1979 Yanoff 1979, Campbell et al 1978) In Chandler s variant the endothelial degeneration is more manifest (Rodrigues et al 1978) Our results show that the specular microscope is a valuable tool for diagnosing EIA

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The clinical specular microscope permits direct observation and evaluation of the corneal endothelial cells in the intact eyeball This instrument was used to study the effects of increased intraocular pressure on the corneal endothelium in various uniocular diseases
The endothelial cell densities of the chronically glaucomatous eyes of 27 patients with uniocular capsular glaucoma were compared with the unaf fected normotensive fellow eyes of the same patients Of these 27 patients, 15 had a lower endothelial cell density in the affected eye than in the healthy fellow eye Ten patients had the same cell density in the affected and cont rol eyes Two patients had a lower cell density in the normotensive eye than in the affected eye The fact that the cell density was lower in 15 of the glaucomatous eyes and higher only in two provides statistically significant confirmation of the direction of the difference
The effects of attacks of increased intraocular pressure on corneal endothelial cell density was studied in 21 patients with uniocular Posner Schloss man syndrome (glaucomatocyclitic crisis) and in 25 patients with unilateral acute glaucoma After attacks of acute glaucoma lasting more than 3 days the endothelial cell density was about 48% lower, but after shorter attacks the endothelial cell density was not significantly affected Attacks of high intraocular pressure in the Posner Schlossman syndrome lowered the cell count and the loss of endothelial cells correlated well with the number of attacks
To ascertain whether keratic precipitates has a deleterious effect especially in the Posner Schlossman syndrome, 60 normotensive (10—20 mmHg) patients with unilateral iridocyclitis were examined Patients with small round keratic precipitates which are similar to those seen in the Posner Schlossman syndrome had approximately the same cell density in both eyes Neither inflammation as such nor the small round keratic precipitates had any effect on the endothelial cell density So in the Posner Schlossman syndrome it is presumably the rises in intraocular pressure that lower the cell count An interesting observation in the chronic iridocyclitic group is that in patients with mutton fat keratic precipitates and severe irido cyclitis 71% of the affected eyes had a distinctly lower endothelial cell density than did the healthy fellow eyes
The state of the corneal endothelial cells was also investigated in 3 patients with the rare condition known as essential iris atrophy In specular micros copy the cells were seen to be large hazy and pleomorphic although in

biomicroscopy the corneas appeared quite normal The specular microscope is a useful aid in differentiating essential iris atrophy from other disorders of the iris

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Paper No I

page 951, lines 10—12 for "Comparison of the above groups showed a statistical difference in the number of glaucoma eyes with a lower cell density (15 lower against 2 higher)", read "The lowered cell densities in 15 glaucomatous eyes and in only two healthy eyes confirms with statistical significance the direction of the difference "

page 956 line 6 for "higher" read "lower"

Paper No II

page 220 in table I enclose "years" in parentheses
page 224, reference No 10, O'Connor G R (1972)

Paper No IV

page 1005, Table I column "difference", rows "Case no 23 24 and 25" for "-4, -2 -–3" read "-1 2, -3"

page 1006, line 11, replace "with no" by "such as"

page 1009 fig 3 magnification is absent Insert "x 500 '

page 1013, line 7 for "cellulkar" read "cellular"

Paper No V

page 1024 line 22 for "guttaca' read "guttaea

page 1025, line 6 for initated read "initiated"

page 1028 line 6 for "dose read "does'

page 1029, line 24 in references for A test and Atlas read A Text and Atlas"



acta ophthalmologica

SUPPLEMENTUM 143

A K. K. K. LUNDSGAARD EDI COEPTA

Medication behaviour a Study of Outpatients treated with Pilocarpine Eye Drops for Primary Open-Angle Glaucoma

by

Staffan Norell



SCRIPTOR COPENHAGEN [illegible]

MEDICATION BEHAVIOUR
A STUDY OF OUTPATIENTS TREATED WITH PILOCARPINE EYE DROPS FOR PRIMARY OPEN-ANGLE GLAUCOMA

Thesis to be defended on February 11, 1980 at Huddinge Hospital by Staffan Norell, Dept of Social Medicine Huddinge University Hospital, S-141 86 Huddinge Sweden

People's behaviour in taking medications is a crucial step in drug treatment Current data suggest that a high proportion of patients on long-term medication do not benefit from their treatment because the drugs are not used correctly The aim of this investigation was to describe the medication behaviour of patients on pilocarpine treatment for glaucoma with special reference to measurement methods patterns of drug-taking, and possibilities of improving medication behaviour

A medication monitor and a fluorescein technique were developed to obtain objective and detailed information on medication behaviour These methods were used 1) to study the medication behaviour of 82 patients with primary open-angle glaucoma for whom pilocarpine eye drops three times daily had been prescribed 2) to evaluate measures aimed at improving medication behaviour in a randomised clinical trial, and 3) to determine the accuracy of patient interviews and estimates by clinical staff in describing medication behaviour

The patients were usually able to administer the eye drops correctly, as indicated by the fluorescein tests However 20-day monitor records showed that 41% of the patients omitted at least 10%, and 20% omitted at least 20% of the doses prescribed Furthermore there was a gradual increase in the number of daily doses missed during a 20-day period between clinic visits For 43% of the patients at least 20% of time was more than 8 hours distant from a previous dose This was due to irregular spacing between the doses taken as well as to missed doses Visual loss from glaucoma during drug treatment is often dealt with by prescribing more potent and more toxic, drugs This may not be appropriate since lack of effect in preventing visual loss may be due to irregular drug taking rather than to the ineffectiveness of the drug

Analysis of the distribution of missed doses showed that doses which were to be taken during the day were missed more than twice as often as morning or evening doses Of the missed doses 54% were second (noon) doses but only 19% were first (morning) doses This suggests that missed doses could be substantially reduced by giving a drug which needs to be taken less often than three times daily

Patient education has often proved insufficient to alter medication behaviour in long-term medication Hence a programme used at the Eye Clinic was based not only on teaching but also on tailoring or integrating the drug regimen into the patient s daily life Evaluation in a randomised clinical trial showed that this programme was effective in altering medication behaviour causing a substantial reduction of missed doses and more regular spacing between the doses taken

Patient interviews are frequently used to obtain information on medication behaviour However comparisons with monitor data showed that underreporting of missed doses is a major problem Less than half the patients not following the prescribed regimen could be identified by interview Estimates by clinical staff were even less accurate

Key words Medication errors - patient participation - patient compliance - pilocarpine - glaucoma

This thesis is based on the following papers referred to in the text by their Poman numerals

I Norell S E Granström P -A and Wassén R A medication monitor and fluorescein technique designed to study medication behaviour Acta Ophthalmologica 58 459 - 467 1980

II Norell S E and Granström P -A Self-medication with pilocarpine among outpatients in a glaucoma clinic British Journal of Ophthalmology 64 137 - 141 1980

III Norell S E Doses prescribed but not taken by the patient Submitted for publication

IV Norell S E Accuracy of patient interviews and estimates by clinical staff in determining medication compliance Social Science and Medicine in pres.

V Norell S E Improving medication compliance a randomised clinical trial British Medical Journal 2 1031-1033 1979

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Key words Medication errors - patient participation - patient compliance - pilocarpine - glaucoma

INTRODUCTION

In recent years much attention has been paid to the patient's role in drug treatment Current data suggest that about 50% of patients on long-term medication do not use their drugs as prescribed[82] This may be one of the major reasons for failure of treatment in such conditions as hypertension[81] heart failure[49] and tuberculosis[19] Consequences include progression of disease and disability[86] medical emergencies[64 93 97] and unnecessary prescriptions of more potent and more toxic drugs Variations in medication behaviour is a major source of error in therapeutic trials[24 30 51] The gap between medical advice and treatment is considered to be a major problem in our health care system[86] In trying to do something about this problem attention has been directed from the patient to his interaction with medical care and to the medical-care system itself

There are several and sometimes contradictory suggestions as to what should be done to improve medication behaviour These suggestions include various changes of the prescribing routines[36 62 72] manipulations of the drug regimen[2 42] or the physical and pharmacological properties of drugs[1 42 63] introduction of special packaging or drug dispensers[23,53 55] serum drug monitoring[6 22 29 35 56 83] the use of various reminders or pill calendars[28 47 76] new systems of labelling[16 46] teaching the patient more about his disease and its treatment[9 13 14 24 45 59 67 81 91] extended supervision[15 32 65 95 98] and making health services more convenient[81] When evaluated in controlled trials however many of these strategies have been found to have little or no effect on medication behaviour[40]

Two major problems in studies of medication behaviour are related to measurement methods Firstly several studies have indicated that the accuracy may be unacceptably low for some of the most commonly used methods including interview[5 33 79] Secondly most of the methods used offer only very rough measures of the patterns of drug-taking such as the average number of missed doses obtained by pill count However the effect of drug treat-

CONTENTS

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ment is not only related to the number of doses taken but also to the spacing between doses Drug plasma levels may give valuable information more closely related to the clinical effects of drug treatment[84] Such information, however, will reflect pharmacokinetic variations as well as variations in medication behaviour[31]

Glaucoma is not only a major cause of blindness, but it is also one of several conditions in which self-medication may prevent serious disease or disability[34 54,73,89,99] Primary open-angle glaucoma often causes only marginal complaints but requires long-term and frequently inconvenient drug treatment This treatment is aimed at preventing long-range damage and provides no subjective improvement to prove its benefit to the patient In fact, drug treatment may even produce temporary symptoms, such as smarting or blurred vision Nevertheless patients are expected to take their medication regularly Moreover, taking the drugs regularly may be of particular importance in glaucoma treatment since the drugs commonly used such as pilocarpine have a relatively short duration of action[21] Little is known about medication behaviour in glaucoma treatment[52] Self-medication has been called the most overlooked aspect of glaucoma"[78]

The objects of the present thesis were

1) To develop measurement methods offering objective and detailed information on the patterns of drug-taking in medication with eye drops

2) To describe medication behaviour with pilocarpine eye drops among patients with primary open-angle glaucoma treated in an eye clinic

3) To determine the accuracy of patient interviews and estimates by clinical staff in describing the medication behaviour of patients treated with pilocarpine

4) To study the effects on medication behaviour of an education and "tailoring" programme for patients on pilocarpine treatment for glaucoma

PATIENTS AND METHODS

Measurement methods (I)

A medication monitor was developed which recorded the date and hour each time the medication bottle was opened The monitor consists of a small plastic box with a holder for a 25-ml bottle for eye drops When the eyedropper cap is removed an elastic flap linked to a microswitch inside the box signals to the electronic part of the monitor The information on whether or not the bottle has been opened during the last hour is transferred to a Random Access Memory with a capacity of 511 hours A record of the total register content can be displayed together with a time signal by connecting the monitor to an electrocardiographic recorder

A fluorescein technique was developed to study the patients abil ty to administer the eye drops into the conjunctival sac Each patient was asked to apply eye drops containing 0 04% fluorescein 5 times in each eye Each time the lacrimal river was examined for the presence of fluorescein using a Haag--Streit-900 slit lamp microscope with a blue filter This gives 10 tests of whether or not the eye drops actually fell into the conjunctival sac

The medication monitor and fluorescein technique were described and discussed in more detail in Paper I

Patients (II-V)

Included were all patients treated at the eye clinic of Huddinge University Hospital by 1 March 1977 who fulfilled the following 6 criteria in their medical records (1) diagnosed as primary open-angle glaucoma with (2) glaucomatous visual-field defects (3) glaucomatous cupping of the optic disc and (4) intraocular pressure above or equal to 21 mm Hg recorded at least twice in the same eye; (5) prescription of 4% pilocarpine eye drops three

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At the second visit the physician seeing the patients estimated their adherence to the pilocarpine regimen Similarly the assistant seeing the experimental group for the patient education and tailoring programme at the end of the second visit estimated these patients adherence to the drug regimen

Fluorescein test were performed after monitor data had been collected and interviews held Of the 82 patients studied 15 patients according to interview always had their pilocarpine eye drops administered by somebody else (5 by a nurse and 10 by relatives) These patients were not examined by the fluorescein technique Another 3 patients were lost to the study before they were tested by the fluorescein technique

A first monitor record was obtained from all 82 patients (For 8 patients a monitor record was obtained only after a second 20-day period owing to defective monitor batteries during the first test period) The second monitor record was lost i 9 cases - one patient suffered acute heart disease two were admitted to hospital for long-term care in two cases the monitor was lost or broken and in four no record was obtained because the monitor battery was defective

Education and tailoring programme (V)

Each patient in the experimental group was seen by an ophthalmology assistant who had been trained for this programme Basic information on the disease and its treatment was supplied in a slide-audiotape format accompanied by a leaflet The assistant checked the patient's knowledge and understanding and re-emphasised insufficiently mastered information The patients were encouraged to ask questions and to discuss problems concerning their own medication Each patient was interviewed by the assistant to find out his or her everyday habits and determine suitable times about eight hours apart when medication could be fitted in with the patients daily routines Whenever poss-

times daily, and (6) visual acuity of at least 2/60 in a pilocarpine-treated eye

Of the 92 patients fulfilling these criteria, 10 were lost before they were studied (Data were collected between March 1977 and November 1978) One patient was lost because he moved abroad 3 because they died, 3 because their therapy was changed, and 3 for psychological or psychiatric reasons The latter 3 refused to visit the clinic and had been out of eye drops for long periods of time during the past few years Medication behaviour of the remaining 82 patients (45 men and 37 women) was studied Their ages ranged from 56 to 90 (median 73) years

Study design and data collection (II-V)

The 82 patients were stratified for age and randomly allocated to an experimental group or a control group Monitor recordings were made over 3 weeks between two visits to the eye clinic The days of the visits were excluded, leaving a monitor record of 20 days for each patient At the second visit to the clinic the patients in the experimental group underwent a 30-minute patient education and tailoring programme (p 9), and the patients in both groups then used the monitor to record their drug-taking for a further 20 days

Patient interviews were held at the end of the second monitor period The patients were not told the purpose of the monitor, until the monitor and interview data had been collected Their informed consent was then obtained, as approved by our local committee on ethics To control other sources of the drug, all prescriptions and bottles of pilocarpine were recalled from the patients when they received the monitor Both groups of patients were treated blind by the attending staff, since the doctor and nurse who saw the patients did not know whether they were in the experimental or in the control group until the end of the second visit

(IV) The physician s and assistant s estimates of their patients adherence to the drug regimen were analysed in relation to the number of doses missed by each patient during the first monitor period Patient interview data on the frequency of missed doses were analysed in relation to the number of missed doses during the 40 days covered by monitor records for each patient in the control group Interview data on the number of missed doses during the past 7 days were compared with the monitor recordings from these days

(V) Evaluation of the patient education and tailoring programme was based on comparisons between the first and the second monitor record from patients in the experimental and in the control group For each patient the proportion of time in each test period that exceeded the 8-hour interval was determined The difference between the first and the second 20-day period was described as a frequency distribution for each group The groups were compared using a t-test and the difference between them was estimated For each patient the proportion of missed doses in each test period was determined Again the difference between the first and the second 20-day period was described as a frequency distribution for each group The groups were compared using a t-test and the difference between them was estimated

RESULTS AND DISCUSSION

Self-medication with pilocarpine (II)

Fluorescein tests were all positive except in one patient who had two negative tests In part this finding may reflect these patients experience in taking eye drops after 0 5 to 23 (median 4 4) years of glaucoma treatment

The 20-day monitor records from 82 patients showed that intervals between doses varied from 1 to 164 hours with a median of 8 hours and a maximum frequency at 6 hours Of the 4542 dose intervals 840 (18%) had a duration of 12 hours or more and 509 (11%) had a

ible, the assistant suggested that the eye drops should be applied immediately before such routines and that the medication bottle should be kept where they were performed The times and routines for medication were written on the leaflet for each patient This programme was described in more detail elsewhere[70]

Analysis of data (II-V)

(II) Medication behaviour of the 82 patients was described on the basis of the first 20-day monitor record obtained from each patient and the results of the fluorescein tests Monitor data were presented as a frequency distribution of dose intervals in hours for the study population If all the prescribed doses had been taken at equal intervals the interval should have been 8 hours For each patient the proportion of time during the test period that exceeded the 8-hour interval was determined The number of missed doses (i e doses prescribed but not taken by the patient) according to the monitor record was determined for each patient and day For each patient the number of missed doses during the 20-day period was divided by the number of doses prescribed, giving the proportion of missed doses

(III) Monitor data were also analysed to describe the distribution of missed doses during the day For each patient there were three different hours (more than two hours apart) during the day when doses were most frequently taken The day was divided into three intervals the first interval lasting up to and including half way between the first and the second of these hours, and so forth Missed doses were classified accordingly as belonging to the 1st (morning) 2nd (noon) or 3rd (evening) interval For the study population the numbers of daily doses missed were analysed in relation to the time elapsed since the last clinic visit

of missed doses found in previous studies and that the time-relationship to clinic visits should be recognised in studies where patient behaviour is involved

Accuracy of patient interviews and estimates by clinical staff (IV)

The number of doses missed by individual patients according to their monitor records did not correlate well with the estimates by the physician (r_s = 0 19 p = 0 08) or the assistant (r_s = 0 30 p 0 05) but somewhat better with patient interview data on the frequency of missed doses (r_s ~ 0 38 p = 0 01) Patient interviews identified 7 out of 16 patients who missed doses at least once a week Underreporting of missed doses was a major problem Of 73 patients interviewed only 4% reported two or more missed doses during the past 7 days whereas monitor records showed that 33% of the patients missed at least two doses and 16% at least six doses during the past week

In clinical practice patient interviews could be used to identify some patients who do not follow the drug regimen prescribed In studies of medication behaviour however interviews may be grossly misleading when used to determine the frequency of missed do es or the proportion of patients not following the prescribed regimen

Effects of patient education and tailoring (V)

In the experimental group there was a striking difference between the frequency distribution of dose intervals during the first and second monitor period Dose intervals of more than 11 hours decreased by 60% and dose intervals of less than 6 hours decreased by 61% In the control group the frequency distribution of dose intervals was similar during both monitor periods

When the two groups were compared patients in the experimental

duration of 4 hours or less

The proportion of time that exceeded the 8-hour dose interval varied from 3 to 88% for individual patients For 35 (43%) of the 82 patients at least 20% of time was more than 8 hours distant from a previous dose The proportion of missed doses varied from 0 to 83% for individual patients Of the 82 patients studie 34 (41%) omitted at least 10% and 16 (20%) omitted at least 20% of the prescribed doses

Visual loss from glaucoma during drug treatment is often dealt with by prescribing more potent, and more toxic drugs This may not be appropriate since lack of effect in preventing visual loss may be due to irregular drug taking rather than to the ineffectiveness of the drug

Distribution of missed doses (III)

A striking finding was that doses which were to be taken during the day were missed more than twice as often as morning or evening doses Of the 507 doses missed by our patients 19% were first (morning) doses 54% second (noon) doses and 27% third (evening) doses This provides indirect evidence that the proportion of missed doses could be substantially reduced by giving a drug which needs to be taken less often than three times daily It is suggested that this should be tested experimentally in different settings where a drug regimen could be altered to reduce the frequency of dosing

When the patients medication behaviour was followed day by day between clinic visits there was a strong correlation (r - 0 85 t = 6 71 p ≅ 0) between missed doses and the time elapsed since the last clinic visit Hence we would arrive at different conclusions about how often doses were missed by our patients depending upon the observation time and the time elapsed since the last clinic visit It is suggested that such differences in observation time could explain some differences in the proportion

Monitor period	Control group (n-38) 1st	2nd	Experimental group (n=35) 1st	2nd
No of missed				
- 1st (morning) doses	52	93	43	36
- 2nd (noon) doses	128	154	105	52
- 3rd (evening) doses	59	91	69	32
Total	239	338	217	120

Table II Distribution of missed doses during the day

GENERAL DISCUSSION AND SUMMARY

The present thesis has focused on three fundamental aspects of medication behaviour namely measurement methods (I IV) analysis of the pattern of drug-taking (II III) and evaluation of measures aimed at improving medication behaviour (V) The investigation was confined to patients with one diagnosis (primary open-angle glaucoma) and one drug regimen (4% pilocarpine eye drops three times daily) This should be kept in mind when comparing the results with findings in previous studies of patients on different kinds of long-term medication

The medication monitor offered objective and detailed information on medication behaviour The accuracy of monitor data was discussed in Paper I and it was suggested that the monitor bottle might be opened for some other purpose than trying to take the drug However extra doses were rarely indicated on the monitor records except in one patient who thought that the drug was to be taken four times daily (II III) Furthermore repeated recordings without intervention showed remarkably constant distributions of dose intervals (V) On the other hand the limited capacity of the monitor memory is a problem since the frequency of missed doses tends to increase over time (III) While our patients were usually able to administer the eye drops correctly (II) this may not be the case among patients with less experience in taking eye drops

group showed a significant decrease in the proportion of missed doses (t = 2 89, p = 0 004) as well as in the proportion of time exceeding 8-hour dose intervals (t = 4 60, p ≅ 0) In both cases, the decrease was estimated at more than half of the levels found during the first monitor period It is concluded that the patient education and tailoring programme was effective in reducing missed doses and time exceeding 8-hour dose intervals

These findings may seem encouraging when compared with some previous findings in controlled trials carried out to evaluate different strategies for improving medication behaviour However, further studies are needed to show to what extent these changes in medication behaviour persist and the effectiveness of the treatment increases

Distribution of missed doses in the experimental study

In addition to the data presented in paper V, the distribution of missed doses in the experimental study was determined (cf III) Table I shows the distribution of days by number of daily doses missed About 2/3 of the reduction in missed doses in the experimental group were accounted for by the decrease in days when one dose was omitted The distribution of missed doses during the day is shown in Table II More than half (55%) of the reduction in missed doses in the experimental group was a decrease in missed second (noon) doses The numbers of doses missed each day were too small to permit analysis of missed doses day by day between clinic visits for each group

	Control group (n=38)		Experimental group (n=35)	
Monitor period	1st	2nd	1st	2nd
No of days when				
- one dose was missed	121	114	126	59
- two doses were missed	23	34	26	20
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The decision to start long-term drug treatment is a serious one exposing the patient to the inconveniences of treatment the possibility of social and psychic trauma the risk of side effects and economic expenses Whether or not the patient will benefit from such treatment depends not only on the effectiveness of the drug regimen prescribed but also on the patient s ability to carry out the treatment

APPENDIX

Medication behaviour or medication compliance ?

Different concepts have been used to describe the actual consumption of a drug prescribed for outpatient treatment Some of these concepts (such as medication behaviour) focus on the patient s drug-taking while others (such as medication compliance) focus on the relationship between the drug regimen prescribed and the patient s drug-taking

Medication behaviour may be defined as a person s behaviour in taking medications In the literature the term medication behaviour [77] has been used interchangeably with self-medication behaviour [7] self-medication [3 12 17 37 44 66 75] and self-administration of drugs/medicaments [27 60 68 85]

Compliance has been defined as the extent to which a person s behaviour (in terms of taking medications following diets or executing lifestyle changes) coincides with medical or health advice [38] Similarly medication compliance may be defined as the extent to which a person s behaviour in taking medications coincides with the drug regimen prescribed In the literature the term medication compliance [4 41 45 81] has been used interchangeably with drug compliance [11 26 61 94] adherence to drug regimens [20] drug-regimen compliance [18] compliance with medication regimens [55] and patient cooperation in taking medicines" [8] Similarly non-compliance in drug treatment i e the discrepancy between medication behaviour and the drug regimen prescribed has been described by terms such as drug deviation [8] dosage deviation [71 77 92] and "drug defaulting [10 69 74]

Patient interviews are often used to obtain information on medication behaviour However, comparisons with monitor data showed that underreporting of missed doses is a major problem Less than half the patients not following the prescribed regimen could be identified by interview Estimates by clinical staff were even less accurate (IV) Similar findings have been reported in previous studies, referred to in Paper IV

Medication behaviour was described on the basis of missed doses (II, III) and the spacing between doses (II) Omitting doses was more frequent than what has been found in previous studies of medication behaviour in glaucoma treatment (II) This is not surprising since the previous studies were based on interview data with underreporting of missed doses as a major problem (IV) On the other hand, our patients missed doses less frequently than what is often indicated by objective data from patients on other kinds of long-term medication[82] This may partly be due to the selection of our patients (II) and the relatively short observation time (III) The proportion of missed doses increased with the time elapsed since the last clinic visit (III) Long duration of dose intervals were often due to irregular spacing between doses, rather than to missed doses (II)

Patient education and tailoring was effective in altering medication behaviour, resulting in a substantial reduction of missed doses and more regular spacing between doses (V) Furthermore analysis of the distribution of missed doses during the day suggests that missed doses may also be reduced by giving a drug which needs to be taken less often than three times daily (III) Both these findings initiated suggestions for further studies

Studies of medication behaviour inevitably raises questions concerning the decision to start (or to continue) drug treatment Although this is beyond the scope of the present thesis the results indicate that a considerable proportion of patients have difficulties in carrying out the drug treatment prescribed Furthermore these patients could not be identified by the clinical staff, and only a minority could be identified by interview

The decision to start long-term drug treatment is a serious one exposing the patient to the inconveniences of treatment the possibility of social and psychic trauma the risk of side effects and economic expenses Whether or not the patient will benefit from such treatment depends not only on the effectiveness of the drug regimen prescribed but also on the patient s ability to carry out the treatment

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The concept "patient compliance" has been widely accepted and used, for example as a heading in Medline and Index Medicus However, this concept has also been discussed and criticised for taking the view of the medical establishment" rather than of the patient[48,87,88,90] Jonsen[50] expressed a wish to criticise compliance because it suggests the ethical 'blooper' of blaming the victim" On the other hand, studies of the "determinants of compliance" have primarily directed attention to the features of the clinical setting and the drug regimen prescribed[39], and successful interventions have been directed towards the delivery of medical services[40]

There is another problem which has attracted much less attention, namely that medication compliance is a far more complex concept than medication behaviour' It is based on (1) the drug regimen prescribed, (2) the medication behaviour, and (3) a comparison between (1) and (2) Such comparisons may introduce problems (e g loss of information) when the data available on (1) and (2) are on different levels, as exemplified in the present thesis

Finally, patients may be more or less aided in their "self--medication , for example by relatives Hence, "medication behaviour" as well as "medication compliance" will be based on social support and supervision in addition to the actions taken by the patient and the prescribing physician

There is a need for concepts to describe a person's behaviour in taking medications, as well as concepts to compare this behaviour with the drug regimen prescribed With the latter we should remember the potential problems related to implicit value judgments and complexity of the concept

Ethical aspects of medication monitoring

Prescribing drug treatment always involves risks as well as potential benefits to the patient The outcome will depend upon the drug regimen prescribed and the patient s ability to carry

out the treatment The impact of medication behaviour (cf p 5) has been recognised since the introduction of objective measurement methods Monitoring of serum drug levels are widely accepted and used and studies of medication behaviour are often based on counts of the remaining tablets urinary excretion of drugs and their metabolites or specific marker substances[31,43] Such methods have been of great value in learning more about the practical problems in drug treatment and in finding measures to improve drug treatment[40]

Our use of the medication monitor had two aims one related to the medical care of the individual patients and the other to medical research All the patients who used the monitor had visual loss from glaucoma many showing progressing loss of vision during drug treatment (II) For these individual patients the monitor offered a means of reviewing and possibly improving their drug treatment without exposing them to any increased risk Our research purpose was to learn more about medication behaviour and how to improve drug treatment in glaucoma Little is known about this although drug treatment is often not effective in preventing visual loss and glaucoma is a major cause of blindness

While the monitor does not expose the patient to any increased risk and offers the possibility of improving the drug treatment for the patient as well as for others there is the question of integrity[96] Informed consent could be obtained (1) before the monitor is given to the patient (2) before the monitor data are printed out by computer and analysed or (3) at a later stage There is strong evidence that (1) would make the results invalid[22 80] According to the second alternative (2) that we used the decision to leave the information on medication behaviour was made by the patient This however did not permit follow-up studies over longer periods of time The procedures were discussed and approved by our local committee on ethics

Suggestions for further studies

Several of the findings reported here gave rise to suggestions

for further studies which, however lie outside the scope of the present thesis They can be divided into three main categories

1) Studies relating medication behaviour to the effectiveness of glaucoma treatment This involves the relationship between medication behaviour and the control of intraocular pressure, mentioned briefly in the Discussion of Paper II Furthermore, and more important, it involves the relationship between medication behaviour and the development of visual-field defects These problems are under investigation in our group

2) Additional studies of medication behaviour in glaucoma treatment As mentioned previously, such studies should preferably be based on inception cohorts (II) and longer observation periods (III) Various drugs are available for glaucoma treatment, and their evaluation and comparison should include studies of medication behaviour Suggestions for further studies on measures aimed at improving medication behaviour are given in Papers III and V With a few exceptions (such as the Health Belief Model) studies relating medication behaviour to various patient characteristics or features of the disease should be given a relatively low priority[39 47]

3) Studies of medication behaviour in conditions other than glaucoma Whenever drugs prescribed for outpatients are effective in the prevention or treatment of disease there is more to learn about medication behaviour and how to improve drug treatment Examples are long-term medication in hypertension epilepsy, and diabetes, to mention but a few While more is known about medication behaviour in these conditions than in glaucoma, there is not much detailed information on the patterns of drug-taking, nor on effective means of improving medication behaviour Some of the methods and results presented in the present thesis may give suggestions for further studies on these problems as exemplified in Papers III and V

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for further studies which, however, lie outside the scope of the present thesis They can be divided into three main categories

1) Studies relating medication behaviour to the effectiveness of glaucoma treatment This involves the relationship between medication behaviour and the control of intraocular pressure, mentioned briefly in the Discussion of Paper II Furthermore, and more important, it involves the relationship between medication behaviour and the development of visual-field defects These problems are under investigation in our group

2) Additional studies of medication behaviour in glaucoma treatment As mentioned previously, such studies should preferably be based on inception cohorts (II) and longer observation periods (III) Various drugs are available for glaucoma treatment and their evaluation and comparison should include studies of medication behaviour Suggestions for further studies on measures aimed at improving medication behaviour are given in Papers III and V With a few exceptions (such as the Health Belief Model), studies relating medication behaviour to various patient characteristics or features of the disease should be given a relatively low priority[39,47]

3) Studies of medication behaviour in conditions other than glaucoma Whenever drugs prescribed for outpatients are effective in the prevention or treatment of disease there is more to learn about medication behaviour and how to improve drug treatment Examples are long-term medication in hypertension, epilepsy, and diabetes to mention but a few While more is known about medication behaviour in these conditions than in glaucoma, there is not much detailed information on the patterns of drug-taking nor on effective means of improving medication behaviour Some of the methods and results presented in the present thesis may give suggestions for further studies on these problems as exemplified in Papers III and V

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SUPPLEMENTUM

acta ophthalmologica

A K. K. K. LUNDSGAARD EDI COEPTA

Effects of Reduced Illumination on the Results Obtained with some Diagnostic Colour Vision Tests in Subjects with Congenital Red-Green Defects

by

Eero Aarnisalo



SCRIPTOR COPENHAGEN 1980

EFFECTS OF REDUCED ILLUMINATION ON THE RESULTS OBTAINED WITH SOME DIAGNOSTIC COLOUR VISION TESTS IN SUBJECTS WITH CONGENITAL RED GREEN DEFECTS

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From the Department of Ophthalmology
University of Turku Finland

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CONTENTS

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INTRODUCTION

The duplicity theory of vision is based on the anatomical observations of Muller (1857) and Schultze (1866) In the vertebrate retina Muller described two types of visual receptors the rods and the cones In his comparative studies Schultze found cones to be predominantly present in the retinae of day animals and rods in night animals the cones thus being daylight receptors and the rods receptors functioning in low illumination The same basic idea was supported by the investigations of the pathology of human night blindness (Parinaud 1881) as well as by the shift in the maximum of the spectral sensitivity curve observed during dark adaptation (von Kries 1896) In his survey of the duplicity theory of vision Hecht (1937) came to the conclusion that all quantitatively measured visual functions may be divided in "photopic" (high luminosity) and in "scotopic" (low luminosity) functions The general conclusion of Barlow (1972) was that typical of the photopic visual function which is mediated by cones containing three different types of photopigments, is a high spatial and temporal resolution a low "Weber fraction" and a capacity to colour discrimination while typical of the rhodopsin based scotopic visual function mediated by the rods is a relatively low spatial and temporal resolution a high "Weber fraction" and the absence of colour vision

In the human eye the photopic visual function is best developed in the central retina with a high number of cones per unit retinal area while the scotopic function is best developed in more peripheral rod dominated areas Between the dominantly photopic and scotopic ranges of visual function remains the somewhat vaguely defined range of "mesopic" visual function

It is difficult to find exact photometric definitions of the limits of the mesopic visual range This is apparently due to the great variations in the experimental techniques used The lower limit of the mesopic range has been reported to vary between the extreme values of 1/40 000 and 1/80 lux (König 1903 von Kries 1916 Rosenberg 1928) or 10^{5} and 3×10^{3} cd/m² (Weaver 1937 Weigell and Knoll 1942 Walters and Wright, 1943 Grigorovici and Ancescu Savopol, 1958) Corresponding values for the upper limits are distributed between 0 2 and 7 ekv lux (Abney and Festing 1892 Dow 1906 Ives 1912), 12 and 150 lux (König 1903 von Kries 1916 Rosenberg 1928 Johnson 1937) 3 and 6

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cd/m^2 (Weaver, 1937, Walters and Wright 1943, Grigorovici and Anceescu Savopol 1958) For practical purposes the lower and upper limits of the mesopic range can be assumed to be 0 001 and 10 cd/m^2 corresponding to a retinal illumination (normal undilated pupil) of 0 044 and 100 trolands (LeGrand 1957)

One of the problems in the study of mesopic vision is the relative contribution of rod and cone functions to the intermediate spectral sensitivity curves The shape of the curve will depend on the retinal area investigated since the receptor population as well as their synaptic connections differ radially Kinney (1955) measured the mesopic spectral sensitivity at luminosity levels 2 3 and 3 5 log units above the scotopic threshold by using a 2 degree test field located on a dark background peripherally at 10 degrees distance from the fovea Her results show that at 2 log units above the absolute threshold the relative sensitivity is first increased in the red end of the spectrum causing a broadening of the base of the curve, but up to 3 5 log units above the threshold the curves remain basically scotopic in shape with little or no shift away from the scotopic maximum at about 510 nm The humps found at 470, 530 and 610 nm in the mesopic curves agreed with those found in the photopic spectral sensitivity curves The evidence of Kinney's results (1955) is that although the mesopic spectral sensitivity curves are basically scotopic in shape, they include definite cone contributions The energy of the strongest test light used (3 5 log units above the scotopic threshold) when evaluated in terms of photopic luminosity was definitely above the photopic threshold of the fovea

Increased illumination saturates the rod function This means that the Weber fraction Δ I/I of the rods is no longer constant but increases The saturation of the rod function begins already within the scotopic illumination range and continues through the mesopic illuminations up to the photopic range Aguilar and Stiles (1954) measured the saturation of the rod function by determining the extrafoveal increment thresholds They used an obliquely directed beam of light passing the edge of a dilated pupil (520 nm test flashes 9° in diameter) superimposed on a directly illuminated (610 nm 20) background thus reducing the effects of the cones In their results Δ I begins to rise steeply and the rod mechanism approaches saturation when the background intensity equals 100 trolands while the rod mechanism appears to be completely saturated at background intensities of 2000 to 5000 scotopic trolands

The reduction of illumination down to the mesopic range alters the colour vision of normal subjects to resemble trichromatic blue yellow defects and further reduction makes the colour vision tritanopic (Grigorovici and Anceescu Savopol 1958) The reduction of illumination to within the scotopic range causes

all colour sensations to disappear The range between the chromatic threshold and the absolute threshold is the photochromatic interval or the "achromatic zone" of Bouman and Walraven (1957) This interval is smallest in the red end of the spectrum (Connors 1969)

The physiological tritan type of colour vision defect, typical of mesopic illuminations emphasizes the special properties of the "blue sensitive system" The existence of blue cones was confirmed by Marks et al (1964) and by Brown and Wald (1964) Both the spatial (Brindley 1954) and temporal (Brindley et al 1966) resolution as well as the flicker fusion frequency of the blue cones is relatively low and their Weber fraction is relatively high (Stiles 1954) Also the total number of the blue cones is relatively low the approximate proportionality between the total number of red green and blue cones being 32 to 16 to 1 (Walraven 1974) In histochemical studies of the baboon retina Marc and Sperling (1977) found that in the central 0 5 degree foveal area only 3 to 4 per cent of cones were blue cones The blue cone density was maximal at 1 degree extrafoveally while the red and green cone densities were maximal in the foveola Stiles (1949) and Brindley (1959) did not find any indication of saturation of the cone function at high physiological intensity levels Recently however the saturation of the blue cones has been demonstrated (Mollon and Polden 1977) and there is also some indication (Shevell 1977) of the saturation of the green and red cones (the π_4 and π_5 mechanisms of Stiles)

As early as 1893 (Ebbinghaus) and 1894 (Konig) both discussed the idea of the rods participating in colour vision as well as the possible interaction processes between the rod and cone mechanisms In fact the relatively high intensity level causing complete saturation of the rod function indicates the simultaneous function of both rods and cones within a large range of light intensities There are several reports on the interaction processes between the rods and blue cones Blackwell and Blackwell (1961) demonstrated the inhibitory effect of the blue cones on the rod function in eyes with incomplete total colour blindness Richards and Luria (1964) who measured colour mixture functions in reduced illumination found evidence of the influence of the rod function on the blue cones They considered the blue cones as an intermediate receptor type with both cone and rod like functional properties The activation of the rod function may give a sensation of bluish colour (Trezona 1970) Hough (1968) investigated the spectral shift from rod to cone dominance caused by increased illumination ("The Purkinje shift" Purkyne 1825) In tritanopic subjects with defective function of the blue cones the Purkinje shift was defective and was completed only at a higher than normal level of light adaptation (Hough and Ruddock 1969 a and b) The subject of rod-cone interactions has been discussed

cd/m² (Weaver, 1937 Walters and Wright 1943 Grigorovici and Aricescu Savopol, 1958) For practical purposes the lower and upper limits of the mesopic range can be assumed to be 0 001 and 10 cd/m² corresponding to a retinal illumination (normal undilated pupil) of 0 044 and 100 trolands (LeGrand 1957)

One of the problems in the study of mesopic vision is the relative contribution of rod and cone functions to the intermediate spectral sensitivity curves The shape of the curve will depend on the retinal area investigated since the receptor population as well as their synaptic connections differ radially Kinney (1955) measured the mesopic spectral sensitivity at luminosity levels 2 3 *and* 3 5 *log* units above the scotopic threshold by using a 2 degree test field located on a dark background peripherally at 10 degrees distance from the fovea Her results show *that at 2 log units above the absolute threshold the relative sensitivity* is first increased in the red end of the spectrum causing a broadening of the base of the curve but up to 3 5 log units above the threshold the curves remain basically scotopic in shape with little or no shift away from the scotopic maximum at about 510 nm The humps found at 470 530 and 610 nm in the mesopic curves agreed with those found in the photopic spectral sensitivity curves The evidence of Kinney s results (1955) is, that although the mesopic spectral sensitivity curves are basically scotopic in shape they include definite cone contributions The energy of the strongest test light used (3 5 log units above the scotopic threshold) when evaluated in terms of photopic luminosity was definitely above the photopic threshold of the fovea

Increased illumination saturates the rod function This *means that the Weber* fraction $\Delta I/I$ of the rods is no longer constant but increases The saturation of the rod function begins already within the scotopic illumination range and continues through *the mesopic illuminations up to the photopic range Aguilar* and Stiles (1954) measured the saturation of the rod function by determining the extrafoveal increment thresholds They used an obliquely directed beam of light passing the edge of a dilated pupil (520 nm test flashes 9° in diameter) superimposed on a directly illuminated (610 nm 20°) background thus reducing the effects of the cones In their results ΔI begins to rise steeply and the rod mechanism approaches saturation when the background intensity equals 100 trolands while the rod mechanism appears to be completely saturated at background intensities of 2000 to 5000 scotopic trolands

The reduction of illumination down to the mesopic range alters the colour vision of normal subjects to resemble trichromatic blue yellow defects and *further reduction makes* the colour vision tritanopic (Grigorovici and Aricescu Savopol 1958) The reduction of illumination to within the scotopic range causes

the test object influences the wavelength discrimination but tritanopia is easier to demonstrate by reduction of the test area This is in agreement with Thomson and Trezona (1951)

The concept of "threshold tritanopia" (Farnsworth 1955) explains the tritanopic effect caused by reduced illumination in terms of a constant quantity of energy (test area × intensity × duration of the test flash) at the threshold Similar ideas had already been proposed by Hartridge (1944 1945 and 1949) According to Farnsworth the threshold tritanopia is not restricted to the fovea only but can be demonstrated in all parts of the retina

The well known relationships between the test area intensity and duration at the visual threshold were described already by Ricco (1877) Bloch (1885) and Piper (1903) The discrimination of colour saturation as a function of the test area was investigated by Walraven (1962) He found that for a test area smaller than 3 the reciprocity between the degree of saturation and the area of test light holds the "Ricco law" of area × intensity = constant, thus being obeyed also in the case of colour perception at the threshold For larger areas the "square root law of Piper" could be applied (Connors 1968) Similar results were obtained by the Yonemura and Kasuya (1969) Weitzman and Kinney (1967 1969) showed that within a certain luminosity range the "law of Bloch" (test area × duration of the test flash = constant) was obeyed In these experiments the diameter of the test area varied within the limits of 11 and 54 and the duration within 20 and 200 msec It also appeared that it was possible to demonstrate tritanopia in normal subjects by shortening the duration of the test light Similar results were obtained by Kaiser (1968) For a normal subject to be able to perceive the colour of a short test flash the shortest duration required is 3 to 4 msec for both blue and red test lights and a much longer time 45 to 66 msec for a yellow test light (Pokorny et al 1979) Siegel (1965) has shown that wavelength discrimination improves with increased duration of the test light, but there is only a slight improvement for durations longer than 0 2 sec

The inconsistent results of colour vision tests can also be due to the use of unusually large test fields Nagel (1905) who himself had deuteranopic colour vision found that an increase in the diameter of the test field of an anomaloscope from the "normal" 3° to 10° altered his equation to indicate a trichromatic anomaly This has been later confirmed in other dichromatic subjects (Jaeger and Kroker 1952 Smith and Pokorny 1977) In subjects with normal colour vision the increased test field of the anomaloscope results in the use of a proportionally larger than normal quantity of red light in order to obtain a satisfactory equation of the red green mixture against yellow (Horner and Purslow 1947 Pokorny and Smith 1976)

in the summaries of Abramov (1972) Jacobs (1976) as well as by Stabell and Stabell (1979 a and b)

König (1894) first demonstrated foveal tritanopia in normal subjects by using small centrally fixated coloured test objects In the human eye the diameter of the entire foveal depression is 1 5 mm corresponding to 5 degrees in the field of view the diameter of the rod free fovea being approximately 0 5 mm or 1°50 in the field of view (Polyak, 1957) The parafovea and perifovea refer to eccentric circular areas extending from 2 5° to 3 5° and from 3 5° to 8 5° respectively (Duke Elder 1961) The size of the test object used to demonstrate foveal tritanopia was 20 (Willmer 1944 Willmer and Wright 1945) 2 (Middleton and Holmes 1949) 3 (MacAdam 1959) 15 to 35 (McCree 1960) less than 20 (Wald, 1967) and 1 24 to 1 47° (Bornstein and Monroe 1978) Slight alterations in the experimental conditions may greatly alter the results (Bedford and Wyszecki, 1958) The origin of the small field tritanopia is not completely clear Apparently the spectral sensitivity for the blue and violet lights of the central fovea is lower than in the surrounding areas (Thomson and Wright 1947, Wald 1967) This is probably due to the very low density or total absence of blue cones in the central fovea (Wald 1967) Willmer (1950) has proposed that the fovea of subjects with protanopia or deuteranopia is monochromatic It has *also been argued that small field tritanopia is due to post receptoral adaptation* processes caused by the central fixation of a small test object (Ingling et al 1970 Ruddock and Burton, 1972)

Already Bezold (1873) Brucke (1878) and Abney (1913) described alterations in colour vision functions caused by reduced illumination Brown (1951) investigating the colourimetric matches of three spectral colours (2° test field central fixation) found that normal colour vision changed to tritanomaly below a critical illumination level of 3 4 cd/m^2 On the other hand Weale (1951) by using a test object of 50 diameter and 3 cd/m^2 luminosity as well as Thomson and Trezona (1951) by using a 1°20 test object at 0 7 to 4 0 log units above the absolute threshold did not find any indication of foveal tritanopia Weale (1951) showed that the reduction of illumination decreased the wavelength discrimination throughout the whole visible spectrum and caused the first discrimination maximum at 490 nm to migrate to 470 nm while the second maximum at 590 to 600 nm remained unaltered This was confirmed by Thomson and Trezona (1951) and McCree (1960) The shift of the first maximum is also apparent in the results of Brown (1951) Tritanopia has been demonstrated at 0 02 cd/m^2 luminosity by using a 75 test object (McCree 1960) and at 0 34 cd/m with a 3° test object (Siegel ano Siegel 1972) The results of McCree (1960) also showed that reduction of either the size or the luminosity of

colour As mentioned above the spectral regions of reduced saturation coincide with those of best wavelength discrimination

Pigment tests of colour vision have been used to study the effects of illumination on the results obtained in normal subjects Using photopic illuminations varying from 300 to 12 000 lux no measurable variation was observed in the results of the Farnsworth Munsell 100 hue test (Cornu and Harlay 1969) According to Sai (1971) the optimal illumination for performing the 100 hue test is 550 lux Middleton and Mayo (1952) used pigment tests to examine the colour vision of normal subjects at reduced illumination They performed tests of colour naming by using the standard Munsell colours (paper chips 2 degrees in diameter) The reduction of the luminance level to 0 13 cd/m² critically altered the results and at 0 013 cd/m² yellow green and blue purple pigments appeared colourless indicating a tritanopic condition At 0 0013 cd/m² only red hues could be perceived Ohta (1957) found that the reduction of the illumination from 200 to 0 6 lux increased the normal average total error score of the Farnsworth Munsell 100 hue test from 12 to 250 Two error maxima observed in low illumination one in red and the other in blue indicated a tritan type of colour vision defect Similar results were obtained by Verriest et al (1963) By using 4 64 lux illumination the two error maxima obtained were located in red (cap number 3) and in blue green (cap number 45) while in 0 046 lux illumination the corresponding maxima were in yellow red (cap number 12) and in blue (cap number 45) indicating scotopization of vision The results of the 100 hue test obtained by Barca and Vaccari (1977 a) and Vola et al (1978) are in agreement with those described above Testing normal subjects with the Panel D 15 dichotomous test, Verriest et al (1963) found tritan type colour confusions at an illumination level of 0 216 lux while scotopization of vision was observed at 0 046 lux

There are very few reports of the effects of reduced illumination on the results of colour vision tests obtained in colour defective subjects Thomson and Trezona (1951) examined wavelength discrimination in normal subjects and in one protanomalous subject. They found low illumination causing a proportionally greater reduction of wavelength discrimination in the protanomalous subject as compared with the normal ones It was also observed that reduced illumination displaced the minimum of the protanomalous wavelength discrimination curve from 490 nm to 470 nm A similar displacement of the minimum of the curve was observed in one deuteranopic subject, caused by a reduction of the illumination from 10 to 0 1 troland (Walraven and Bouman 1966) Unfavourable conditions, like low illumination a small test field and short exposure time may reduce the colour vision of anomalous trichromats

Most of the basic knowledge of colour (wavelength) discrimination in normal and colour defective subjects has been obtained in colourimetric measurements made with spectral lights The standard procedure is to illuminate two halves of a test field each with a beam of light from a monochromator One half of the field is used as a reference at a fixed wavelength while the colour of the other field is changed (and the luminance compensated) until a difference in the perceived colour between the two fields can be noticed The wavelength discrimination curve of normal observers (Wright and Pitt 1934) shows three minima near 445, 495 and 595 nm The wavelength discrimination is best (1 to 2 nm) in the blue green and orange yellow and there is a third less prominent minimum in the blue violet In both protanopic and deuteranopic subjects the best discrimination (2 to 4 nm) is found at 490 to 500 nm while on both sides of the blue green region the discrimination curve shows a steep rise (Wright, 1946) In subjects with a trichromatic red green anomaly, Nelson (1938) and McKeon and Wright (1940) found two spectral regions of good discrimination one at 490 to 500 nm and the other at 600 nm In tritanopic subjects the best discrimination is found in the violet region at about 420 nm and in the yellow region at 580 to 590 nm (Wright 1952)

In colour defective subjects the perceived saturation of the colour is lowest in the spectral regions of best wavelength discrimination (Pitt 1935) The neutral areas of protanopic and deuteranopic subjects are at about 485 to 495 and 495 to 505 nm respectively (Walls and Heath, 1956, Massof and Bailey, 1976) In tritanopia the neutral areas are located at about 410 and 580 nm (Wright 1952 Krill et al 1970) In tetartanopia a more or less theoretical condition (Linksz 1964) the neutral areas have been located at 480 and 570 nm (Wright 1952) In subjects with trichromatic anomalies the spectral regions of reduced saturation correspond to the neutral regions of dichromatic subjects (Chapanis 1944)

The Farnsworth Munsell 100 hue test (Farnsworth 1943) measures wavelength discrimination with the pigment colours of Munsell In the present modification (Farnsworth 1957) of this test, there are 85 coloured papers (2 degrees diameter at 33 cm viewing distance) of equal photopic luminance and saturation A reduced wavelength discrimination of the red green defectives can be demonstrated as bipolar groupings of errors in the yellow and blue green regions respectively The H R R (Hardy et al 1954 a) test measures the ability to discriminate the saturation of pigment colours but in fact all pigment tests detecting colour confusions the Panel D 15 dichotomous test (Farnsworth 1947) as well as the pseudo isochromatic tests are based on the fact that there are in the colour defective subjects bipolar regions of reduced saturation of the

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to approaching dichromatic conditions (LeGrand, 1957) By using colour *naming tests with a test field of 54' diameter 200 msec duration and 0 6 cd/m²* luminance, in two deuteranopic subjects examined by Weitzman and Kinney (1967) the colour vision was nearly monochromatic No sensation of colour was *perceived by these subjects when the size and duration of the test field* was further reduced In one deuteranopic subject examined by Luria (1967) with the colour naming test (test field of 45' diameter, 20 msec duration and 0 5 cd/m² luminance) the result was similar Verriest and Uvijls (1977) measured central and peripheral spectral sensitivity functions both in normal and colour defective subjects, and observed in the latter abnormally high foveal thresholds for white light They also found in the central visual field of the colour defective subjects abnormally high thresholds for blue light when measured by using a relatively low (3 16 cd/m²) background luminance level

Schmidt (1952) examined colour defective subjects with the pseudo isochromatic tests of Ishihara and American Optical Company (AOC) Illumination, increased from 270 to 1000 lux, improved the results The largest improvement was observed in deuteranomalous subjects Hill et al (1978) used ten different colour vision tests including the Farnsworth Munsell 100 hue and Panel D 15 dichotomous tests, as well as the H R R and Ishihara tests to examine colour defective subjects Illumination, varying within the range of 200 to 600 lux, had no effect on the results obtained

Walraven and Leebeek (1960) investigated the effects of reduced illumination on the colour vision of colour defective subjects They varied the illumination from 500 to 0 1 lux and examined the ability of colour defective subjects, also classified by the H R R and Ishihara tests, to recognize colour coded electric resistors Subjects with defects classified as "mild by the H R R test obtained results comparable to those obtained by normal subjects at six times lower *illumination* It was also observed that in reduced illumination the colour defectives as compared with normal subjects made proportionally more blue yellow than red green mistakes

THE PRESENT STUDY

The purpose of the present study was to investigate alterations in the results of pigment tests of colour vision caused by the reduction of illumination A series of normal subjects and subjects with congenital red green defects of colour vision were examined Illumination levels varying between photopic 200 cd/m² and mesopic 0 02 cd/m² were used The Farnsworth Munsell 100 hue test was employed to investigate discrimination and the Panel D 15 dichotomous test and Boström Kugelberg (1972) pseudo-isochromatic plates were used to test colour confusions The classification of types and degrees of the red green defects was performed with the aid of the Nagel anomaloscope The final series selected comprised 30 cases of deuteranomaly (DA) 26 cases of extreme deuteranomaly (EDA) 13 cases of deuteranopia (D) 11 cases of protanomaly (PA) 10 cases of extreme protanomaly (EPA) 10 cases of protanopia (P) and 30 normal subjects (N)

MATERIAL

The series of colour defective and normal subjects were collected in four preliminary screenings using somewhat varying methods.

In the first screening 350 University students were examined using a combination of the Boström Kugelberg (BK I 1944) and Boström (II B 1950) pseudo isochromatic tests No errors were allowed

In the second screening 750 pupils from a technical school were examined using the Boström Kugelberg (BK II 1972) pseudo isochromatic test In all borderline cases (one error made in the BK II test) all plates of the additional Boström (II B) test (no errors allowed) were shown

In the third screening military personnel examined 1250 conscripts at two garrisons using one of the two Ishihara pseudo isochromatic tests available In the 24 plates edition (1960) 2 errors were allowed while in the complete 38 plates edition (1973) 4 errors were allowed An additional 900 conscripts were examined in a fourth screening (also employing the Ishihara tests) in order to increase, in the final series the number of protanopes

All subjects not passing the preliminary screenings were examined with the Nagel anomaloscope In all subjects thus selected a conventional ophthalmological examination was also performed Subjects with a corrected visual acuity in the worse eye of below 1 0 were excluded and so were subjects with a refractive error of more than –3 0 D This was considered to exclude cases with myopic pseudoprotanomaly (Verriest 1964) To exclude other types of acquired defects of colour vision an ophthalmoscopy of the macular area was performed Also excluded were subjects with an apparent squint as well as subjects with a defective (without glass correction) reading visual acuity at 30 to 40 cm distance Also the normal subjects passed all the tests mentioned above

The final series selected comprised 100 colour defective and 30 normal subjects They were all healthy young men aged 18 to 28 (colour defective subjects) and 21 to 29 (normal subjects) At this age both the colour defective and normal subjects give their best performance in colour vision tests (Lakowski 1958, Verriest et al 1962 Lakowski 1974 Barca and Vaccari 1977 b) 57 per cent of the colour defective subjects and 50 per cent of normal subjects were students at the University or had a University degree

METHODS

The Nagel anomaloscope (Model I Schmidt & Haensch Berlin) was used for the classification of the types and degrees of the red green defects Two instruments serial numbers 17731 and 17582 were used A series of normal subjects were examined to establish the average normal mid matching point (MP 44 30 and 44 53 respectively) of both instruments For practical reasons 44 5 was selected to represent the MP of normal subjects The normal MP was repeatedly checked in the course of the study

In the standard anomaloscope examination procedure as described by Linksz (1964) and Heinsius (1973) and also used in the present study the subject looks at the coloured circular test field (2°10 in diameter horizontally divided into two equal halves) for periods of no more than 3 seconds interrupted by periods of 10 seconds of looking at the white conditioning field of the instrument When the mid matching point and the matching range (MR) have been found the subject is allowed to look continuously (over 15 seconds) at the coloured test field and the effect of colour conditioning on the matching range is examined The examiner systematically alters the position of the red green control knob while the subject tries to find a match for the two field halves If necessary the luminosity of the yellow (lower) field is altered from the standard position at 14 scale divisions of the yellow control knob The matching range is measured by rotating the red green control in steps of 10 to 2 scale divisions and when the *approximate limits* have been estimated they are measured more accurately by rotating the control knob in steps of a one scale division The mid matching point represents the midpoint of the matching range obtained in the eye conditioned to white light. In the present work the term extreme anomaly" is applied only to subjects showing a *matching range* at least 10 scale divisions (red green control) larger in the colour conditioned eye than in the eye conditioned to the white light (Helve 1972) I performed all the anomaloscope examinations personally *The subject* was asked to use his "better" eye as he himself *preferred*

The Macbeth daylight illuminator (Macbeth Executive BBX 324 Kollmorgen Ltd, Switzerland) was used in all tests with colour pigments *These tests included* the Farnsworth Munsell 100 hue test (*Munsell Color* Company Baltimore), the Panel D 15 dichotomous test (*The* Psychological Corporation New York) and

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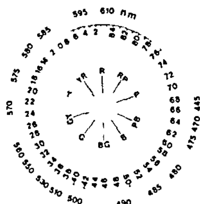


Fig 1

Diagram of the colour circle of the Farnsworth Munsell 100-hue test (F100) showing distribution of the colour caps in their relation to the dominant wavelength (nm) of the colour

number of that cap and the numbers of caps adjacent to it The total error score (ST) is obtained by adding the individual scores after subtracting 2 from each individual score According to Farnsworth normal subjects with superior average or low ability to discriminate colours obtain in this test total error scores of below 20 within the range 20 to 100 or above 100 respectively To make it possible to evaluate mathematically the typically bipolar pattern of the result plotted on the circular scale the scale can be divided into four quadrants showing a maximum of totalled error scores in two opposite quadrants and a minimum of totalled error scores in the two remaining quadrants From the results obtained in subjects with dichromatic colour vision Hukami and Ichikava (1969) and Helve (1972) computed the position of the lines dividing the colour circle into four quadrants in a way that gave the maximum value for the ratio of the total error scores of quadrants I (yellow hues) and III (blue and purple hues) to the totalled error scores of quadrants II (green and bluish hues) and IV (red hues) Typically in cases of red green defects, a large error score is obtained in quadrants I and III and a small error score in quadrants II and IV In the present study the colour circle was initially divided into two halves including colour caps 79 to 35 and 36 to 78 respectively On the side of the bluish purple hues (36 to 78) the computed line of division pointed to 59 8 (average error score maximum of protanopes) and 57 8 (average error score maximum of deuteranopes) To facilitate treatment of results a single line of division (cap 59) was chosen The quadrants used in the present study were established by this line in the following way quadrant I caps 7 to 27 quadrant II caps 28 to 48 quadrant III caps 49 to 69 quadrant IV caps 70 to 6 (Figs. 6 and 7 D200 and P200)

the Bostrom Kugelberg pseudo isochromatic test (Ab Nordiska Bokhandelns Forlag, Stockholm) All these tests were performed binocularly at normal reading distance (30–40 cm) Two Macbeth daylight illuminators, serial numbers MB 1128 and MB 1350, were used The colour temperature of the 'North Sky Daylight" of this instrument is 7500°K The illumination at the horizontal desk of both instruments as measured in the midline at 10 cm distance from the front margin with a 'Hagner universalljusmatare modell S 1" (B Hagner, Solna Sweden) was 1800 lux the corresponding luminosity of this matte gray surface being 195 (MB 1350) and 200 cd/m² (MB 1128) The latter value is used below Measured at the same location the luminosity of the coloured papers of both the Farnsworth Munsell 100 hue and the Panel D 15 dichotomous tests was 120 cd/m² According to Connors (1964) and Siegel (1969) a luminosity decrement of 0 6 magnitude between the colour and the background favours the obtaining of reliable results in the colour discrimination tests The luminosity of the coloured spots of the Bostrom Kugelberg pseudo isochromatic test varied between 370 and 420 cd/m² the luminosity of the white background of the plates being 500 cd/m²

The Farnsworth Munsell 100 hue test (F100 Farnsworth 1943 and 1957) offers a practical method for testing colour discrimination The test consists of a circle of 85 Munsell coloured papers in which the hue differences can just be discerned by normal subjects when the papers are suitably mounted This mounting consists of plastic caps with black rims which separate the exposed part of the colour discs by their own diameter (12 mm) These 85 colours as plotted on the Farnsworth chromaticity diagram are placed at approximately equal distances around the point C, the saturation of the different colours being roughly identical The colour caps are grouped in four sections (85 to 21, 22 to 42, 43 to 63 and 64 to 84) The colours (dominant wavelength) are not equally distributed over the spectrum In fact there is a concentration of colour caps in the spectral regions of good normal colour discrimination (blue green and yellow orange regions) while there is a much lower number of colour caps in the regions of low normal colour discrimination (Fig 1)

The object of the test is to arrange the caps in order according to the colour The subject finds the caps in a random order, and arranges them in a sequence between two fixed pilot colour caps The four wooden boxes (each containing a quarter of the test colours) may be presented in any order the average time required to arrange the colours of one box being two minutes The result of the test is scored on a circular diagram with radii numbered 1 to 85 which intersect concentric rings numbered 2 to 14 In the present study an extended diagram (Fig 5) was used The score for a cap is the sum of the differences between the

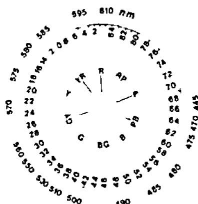


Fig 1

Diagram of the colour circle of the Farnsworth Munsell 100 hue test (F100) showing distribution of the colour caps in their relation to the dominant wavelength (nm) of the colour

number of that cap and the numbers of caps adjacent to it. The total error score (ST) is obtained by adding the individual scores after subtracting 2 from each individual score According to Farnsworth normal subjects with superior average or low ability to discriminate colours obtain in this test total error scores of below 20 within the range 20 to 100 or above 100 respectively To make it possible to evaluate mathematically the typically bipolar pattern of the result plotted on the circular scale the scale can be divided into four quadrants showing a maximum of totalled error scores in two opposite quadrants and a minimum of totalled error scores in the two remaining quadrants From the results obtained in subjects with dichromatic colour vision Hukami and Ichikava (1969) and Helve (1972) computed the position of the lines dividing the colour circle into four quadrants in a way that gave the maximum value for the ratio of the total error scores of quadrants I (yellow hues) and III (blue and purple hues) to the totalled error scores of quadrants II (green and bluish hues) and IV (red hues) Typically in cases of red green defects a large error score is obtained in quadrants I and III and a small error score in quadrants II and IV In the present study the colour circle was initially divided into two halves including colour caps 79 to 35 and 36 to 78 respectively On the side of the bluish purple hues (36 to 78) the computed line of division pointed to 59 8 (average error score maximum of protanopes) and 57 8 (average error score maximum of deuteranopes) To facilitate treatment of results a single line of division (cap 59) was chosen The quadrants used in the present study were established by this line in the following way quadrant I caps 7 to 27 quadrant II caps 28 to 48 quadrant III caps 49 to 69 quadrant IV caps 70 to 6 (Figs 6 and 7 D200 and P200)

the Bostrom Kugelberg pseudo isochromatic test (Ab Nordiska Bokhandelns Forlag, Stockholm) All these tests were performed binocularly at normal reading distance (30–40 cm) Two Macbeth daylight illuminators, serial numbers MB 1128 and MB 1350 were used The colour temperature of the "North Sky Daylight" of this instrument is 7500°K The illumination at the horizontal desk of both instruments, as measured in the midline at 10 cm distance from the front margin with a "Hagner universalljusmatare modell S 1" (B Hagner, Solna Sweden) was 1800 lux, the corresponding luminosity of this matte gray surface being 195 (MB 1350) and 200 cd/m^2 (MB 1128) The latter value is used below Measured at the same location the luminosity of the coloured papers of both the Farnsworth Munsell 100 hue and the Panel D 15 dichotomous tests was 120 cd/m^2 According to Connors (1964) and Siegel (1969) a luminosity decrement of 0 6 magnitude between the colour and the background favours the obtaining of reliable results in the colour discrimination tests The luminosity of the coloured spots of the Bostrom Kugelberg pseudo isochromatic test varied between 370 and 420 cd/m^2, the luminosity of the white background of the plates being 500 cd/m^2

The Farnsworth Munsell 100 hue test (F100 Farnsworth 1943 and 1957) offers a practical method for testing colour discrimination The test consists of a circle of 85 Munsell coloured papers in which the hue differences can just be discerned by normal subjects when the papers are suitably mounted This mounting consists of plastic caps with black rims which separate the exposed part of the colour discs by their own diameter (12 mm) These 85 colours as plotted on the Farnsworth chromaticity diagram are placed at approximately equal distances around the point C, the saturation of the different colours being roughly identical The colour caps are grouped in four sections (85 to 21 22 to 42 43 to 63 and 64 to 84) The colours (dominant wavelength) are not equally distributed over the spectrum In fact there is a concentration of colour caps in the spectral regions of good normal colour discrimination (blue green and yellow orange regions), while there is a much lower number of colour caps in the regions of low normal colour discrimination (Fig 1)

The object of the test is to arrange the caps in order according to the colour The subject finds the caps in a random order and arranges them in a sequence between two fixed pilot colour caps The four wooden boxes (each containing a quarter of the test colours) may be presented in any order the average time required to arrange the colours of one box being two minutes The result of the test is scored on a circular diagram with radii numbered 1 to 85 which intersect concentric rings numbered 2 to 14 In the present study an extended diagram (Fig 5) was used The score for a cap is the sum of the differences between the

	P ksi	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
				Tr	Tr	Tr	Te	Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr
P ksi					Tr	Tr	Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr	Pr
1						Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr	Pr	De
2							Te	Te	Te	Pr	Pr	Pr	Pr	Pr	De	S
3	Tr							Te	Pr	Pr	Pr	Pr	Pr	De	De	S
4	Tr	Tr							Pr	Pr	Pr	Pr	De	De	S	S
5	Tr	Tr	Te							Pr	De	De	De	S	S	Te
6	Te	Te	Te	Te							De	S	S	S	Tr	Tr
7	Te	Te	Te	Te	Te							S	S	Tr	Tr	Tr
8	Te	Te	Te	Te	Pr	Pr							Tr	Tr	Te	Te
9	Te	Te	Pr	Pr	Pr	Pr	Pr							Te	Te	Te
10	Te	Pr	Pr	Pr	Pr	Pr	De	De							Te	Te
11	Pr	Pr	Pr	Pr	Pr	Pr	De	S	S							Te
12	Pr	Pr	Pr	Pr	Pr	De	De	S	S	Tr						
13	Pr	Pr	Pr	Pr	De	De	S	S	Tr	Tr	Te					
14	Pr	Pr	Pr	De	De	S	S	Tr	Te	Te	Te	Te				
15	Pr	Pr	De	S	S	S	Tr	Tr	Tr	Te	Te	Te	Te			

Table 1

The relationship between the *two ends of confusion lines (number of cap horizontal and vertical) obtained in* the Panel D 15 dichotomous test (F 15) and calling the type of the confusion protan (Pr) deutan (De), scotopic (S) tritan (Tr) and tetartan (Te). All possible confusion axes which may appear *in the F-15 test* can be described and named by using this diagram.

The Panel D 15 dichotomous test (F15, Farnsworth 1943 and 1947) is designed to indicate colour blindness 'clearly and quickly i e to distinguish the functionally colour blind from those with moderate colour blindness or normal colour vision Most subjects with mild defects of colour vision are known to pass the test without errors (Hardy et al 1954 b, Crone 1961) while subjects with dichromatic colour vision fail in this test (Verriest, 1968 Dreyer 1969, Majima 1969, Helve, 1972) The equipment consists of 15 colour caps and one (blue) pilot colour cap fixed at one end of the panel The F15 test colours as plotted on the Farnsworth chromaticity diagram are situated at approximately equal distances around point C, the saturation of the different test colour being roughly identical The black surrounding rim and the exposed area of the colour discs are identical to those of the colour caps of the F100 test The object of the test is to arrange the removable colour caps in order according to colour The subject first has to choose the colour cap which appears most like the blue reference colour Next he has to place beside it the colour cap, which is most like the one previously chosen and to continue in the same way until he has arranged all the caps in line Thus the arrangement depends wholly on the perceived colour of each cap and its relative likeness to the other test colours The subject is not asked to name or describe colours The average time required to arrange the caps is two minutes The test is scored on a diagram (Fig 2) with numbers 1 to 15 referring to the respective colour caps The numbers of the diagram are connected with lines according to the order in which the caps were arranged A circular pattern means 'pass" and a parallel or lacing pattern means 'fail The

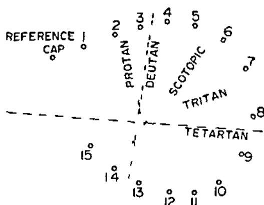


Fig 2
Diagram of the distribution of the numbers of colour caps of the Panel D 15 dichotomous test (F15) showing their relation to the directions of typical protan deutan scotopic tritan and tetartan confusion axes used in the scoring of this test (see methods)

	Pilot	1		3	4	5	6	7	8	9	10	11	12	13	14	15
Pilot				Tr	Tr	Tr	Te	Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr
1					Tr	Tr	Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr	Pr
2						Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr	Pr	De
3	Tr						Te	Te	Te	Pr	Pr	Pr	Pr	Pr	De	S
4	Tr	Tr						Te	Pr	Pr	Pr	Pr	Pr	De	De	S
5	Tr	Tr	Te						Pr	Pr	Pr	Pr	De	De	S	S
6	Te	Te	Te	Te						Pr	De	De	De	S	S	Tr
7	Te	Te	Te	Te	Te						De	S	S	S	Tr	Tr
8	Te	Te	Te	Te	Pr	Pr						S	S	Tr	Tr	Tr
9	Te	Te	Pr	Pr	Pr	Pr	Pr						Tr	Tr	Te	Te
10	Te	Pr	Pr	Pr	Pr	Pr	De	De						Te	Te	Te
11	Pr	Pr	Pr	Pr	Pr	Pr	De	S	S						Te	Te
12	Pr	Pr	Pr	Pr	Pr	De	De	S	S	Tr						Te
13	Pr	Pr	Pr	Pr	De	De	S	S	Tr	Tr	Te					
14	Pr	Pr	Pr	De	De	S	S	Tr	Tr	Te	Te	Te				
15	Pr	Pr	De	S	S	S	Tr	Tr	Tr	Te	Te	Te	Te			

Table 1

The relationship between the two ends of *confusion lines* (number of cap horizontal and vertical) obtained in the Panel D 15 dichotomous test (F15) indicating the type of the confusion protan (*Pr*), *deutan* (*De*), *scotopic* (*S*), tritan (Tr) and tetartan (Te). All possible confusion axes which may appear in the F15 test can be described and named by using this diagram

The Panel D 15 dichotomous test (F15, Farnsworth 1943 and 1947) is designed to indicate colour blindness "clearly and quickly" i e *to distinguish the* functionally colour blind from those with moderate colour blindness or normal colour vision Most subjects with mild defects of colour vision are known to pass the test without errors (Hardy et al 1954 b, Crone 1961), while subjects with dichromatic colour vision fail in this test (Verriest, 1968 Dreyer 1969, Majima 1969, Helve, 1972) The equipment consists of 15 colour caps and one (blue) pilot colour cap fixed at one end of the panel The F15 test colours as plotted on the Farnsworth chromaticity diagram are situated at approximately equal distances around point C, the saturation of the different test colour being roughly identical The black surrounding rim and the exposed area of the colour discs are identical to those of the colour caps of the F100 test The object of the test is to arrange the removable colour caps in order according to colour The subject first has to choose the colour cap which appears most like the blue reference colour Next he has to place beside it the colour cap, which is most like the one previously chosen and to continue in the same way until he has arranged all the caps in line Thus the arrangement depends wholly on the perceived colour of each cap and its relative likeness to the other test colours The subject is not asked to name or describe colours The average time required to arrange the caps is two minutes The test is scored on a diagram (Fig 2) with numbers 1 to 15 referring to the respective colour caps The numbers of the diagram are connected with lines according to the order in which the caps were arranged A circular pattern means "pass" and a parallel or lacing pattern means "fail" The

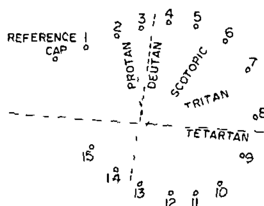


Fig 2

Diagram of the distribution of the numbers of colour caps of the Panel D 15 dichotomous test (F15) showing their relation to the directions of typical protan deutan scotopic tritan and tetartan *confusion axes used in the* scoring of this test (see methods)

	Pilot	1		3	4	5	6	7	8	9	10	11	12	13	14	15
Pilot				Tr	Tr	Tr	Te	Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr
1					Tr	Tr	Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr	Pr
2						Te	Te	Te	Te	Pr	Pr	Pr	Pr	Pr	Pr	De
3	Tr						Te	Te	Te	Pr	Pr	Pr	Pr	Pr	De	S
4	Tr	Tr						Te	Pr	Pr	Pr	Pr	Pr	De	De	S
5	Tr	Tr	Te						Pr	Pr	Pr	Pr	De	De	S	S
6	Te	Te	Te	Te						Pr	De	De	De	S	S	Tr
7	Te	Te	Te	Te	Te						De	S	S	S	Tr	Tr
8	Te	Te	Te	Te	Pr	Pr						S	S	Tr	Tr	Te
9	Te	Te	Pr	Pr	Pr	Pr	Pr						Tr	Tr	Te	Te
10	Te	Pr	Pr	Pr	Pr	Pr	De	De						Te	Te	Te
11	Pr	Pr	Pr	Pr	Pr	Pr	De	S	S						Te	Te
12	Pr	Pr	Pr	Pr	Pr	De	De	S	S	Tr						Te
13	Pr	Pr	Pr	Pr	De	De	S	S	Tr	Tr	Te					
14	Pr	Pr	Pr	De	De	S	S	Tr	Tr	Te	Te	Te				
13	Pr	Pr	De	S	S	S	Tr	Tr	Tr	Te	Te	Te	Te			

Table 1

The relationship between the two ends of confusion lines (number of cap horizontal and verti al) *obtained in the Panel D 15 dichotomous test* (F15) *indicating the type of the confusion* protan (Pr) deutan (De) scotopic (S) *tritan (Tr) and* tetartan (Te). All possible confusion axes which may *appear in the F15 test* can be described and *named* by using this diagram

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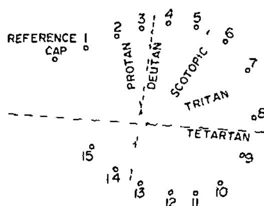


Fig 2

Diagram of the distribution of the numbers of colour caps of the Panel D 15 dichotomous test (F15) showing their relation to the directions of typical protan deutan scotopic tritan and tetartan confusion axes used in the scoring of this test (see methods)

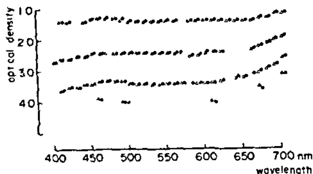


Fig 3

Optical densities of the pairs of neutral filters used. Black dots filters used on the right side (displaced 5 nm to the right on the wavelength scale). Triangles filters of the left side

filter	background	background	retinal illumination
optical density	illumination lux	luminosity cd/m²	troland
0 0	1800	200	1150
1 3	90	10	100
2 3	9	1	15
3 3	0 9	0 1	1 95
4 0	0 18	0 02	0 72

Table 2

Optical densities of the neutral filters used in the present study Also the corresponding background illuminations (lux) and luminosities (cd m) of the Macbeth daylight illuminator and the retinal illumination levels (normal undilated pupil) expressed in trolands are shown

filters in four identical pairs of lightproof (matte black inside the frame) welders glasses (Amigo Sweden) The subjects did not wear their regular eye glasses Spectrophotometric (Jarrel Ash M 75 150 Technical Research Centre of Finland) measurements of the filter densities are illustrated in Fig 3 and Table 2 shows the approximate light energy levels of the Macbeth daylight illuminator as well as the corresponding retinal illuminations at the five different illumination levels used (LeGrand, 1957).

patterns of colour blind subjects will in general form a series of parallel or criss cross lines with at least two lines crossing the chart in approximately the same direction The patterns of normal subjects may some times show a single crossing line which occurs when part of the series is started in reverse or they may show one or two transpositions of adjacent caps (minor errors) Three typical directions of crossing lines protan deutan and tritan are indicated on the original chart Verriest et al (1963) have completed the chart by adding lines indicating tetartan and scotopic directions (Fig 2) In the present work the completed chart was used and the procedure was further modified The deutan tetartan and scotopic lines were displaced parallel to their original direction in order to make them intersect the crossing point of the protan and tritan lines (reference point of the present study) which is located close to point C in the Farnsworth chromaticity diagram The protan axes was then chosen to represent the zero direction the other directions deviating from the zero position as follows, deutan 15 5°, scotopic 40 5°, tritan 79 5° and tetartan 103° The angles between the lines indicating the directions were divided into halves the sectors referring to the different types of defects thus established protan 38 5 to 7 75°, deutan 7 75 to 28°, scotopic 28 to 60°, tritan 60 to 91 25° and tetartan 91 25 to 141 5° The angular deviation from the zero (protan) axes of all possible confusion axes appearing in these F15 test (displaced parallel to their original direction to intersect the reference point) was then calculated and related to the sectors described above (Table 1)

The plates of the Bostrom Kugelberg pseudo isochromatic test (BKII Kugelberg 1972) used in the present study all show a number formed of coloured spots on a background of coloured spots All figures of this colour confusion test are of the 'vanishing type The colours have been chosen from the pseudo isochromatic lines but their exact colourimetric values are not known In the present study only 15 plates with figures of numbers were used and the other plates (two plates with serpent figures and three dissimulation plates) were excluded The separate plates were mounted and shown on a background (17 × 20 cm) of white paper According to the original instructions normal subjects make no errors in this test One error indicates a borderline case and two errors indicate defective red green colour vision Some mild red green defectives may pass the test without errors (Hedin 1974 Aarnisalo 1979)

All tests with colour pigments employing the Macbeth daylight illuminator were performed in darkened rooms with black or dark gray walls Four different rooms were used Neutral density filters series NG 4 and NG 9 (Jenaer Glaswerk Schott & Gen Mainz) were used to alter the illumination level Equal pairs of filters optical densities (at 546 nm) 1 3 2 3 3 3 and 4 0 were used to replace the

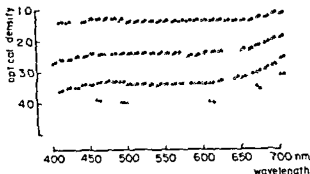


Fig 3

Optical dens ties of the pairs of neutral filters used Black dots filters used on the right side (displaced 5 nm to the right on the wavelength scale). Triangles filters of the left side

filter	background	background	retinal illumination
optical dens ty	illumination lux	luminosity cd/m²	troland
0 0	1800	700	1150
1 3	90	10	100
2 3	9	1	15
3 3	0 9	*0 1*	*1 95*
4 0	0 18	0 0[illegible]	0 72

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Optical dens ties of the neutral filters used in the present study Also the *corresponding background* i m nations (lux) and lum nos t es (cd m²) of the Macbeth daylight illuminator and the retinal il mination le els (normal und lated pupil) expressed in trolands are shown

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The complete Farnsworth 100 hue test was performed only at illumination levels 200 cd/m^2 (no filters used) and at 0 1 cd/m^2 (filter density 3 3) At 10 1 and 0 02 cd/m^2 only the caps of the first box of the F100 test (B_1 caps 85 to 21) were presented The BKII pseudo isochromatic plates and the Panel D 15 test *were performed* at all five illumination levels *Only 15 plates (figures of numbers)* of the BKII test were shown The plates were exposed for 10 seconds and the test was not repeated Next followed the F15 and the F100 tests The subject was allowed to correct the result of both these tests but the test was not repeated The tests performed at subsequent illumination levels were interrupted only during the time taken to change the filter glasses This was done in a dim red light the Macbeth illuminator was cut off during the time taken to change the glasses Only at the illumination levels 0 1 and 0 02 cd/m^2 was 3 minutes of adaptation allowed *before the tests* were *begun The whole test procedure including the* preliminary anomaloscope and standard ophthalmological examinations took about two hours to perform I myself performed all the examinations with the pigment tests, a technical assistant contributed to about one third of the examinations

RESULTS

Results obtained with the Nagel anomaloscope by 100 subjects with defective colour vision and by 30 normal subjects are illustrated in Fig 4 The horizontal bars of the left column refer to the matching range (MR) obtained in the eye conditioned to white light, while the bars of the right column refer to the MR obtained in the eye conditioned to the coloured test field of the anomaloscope The letters n and u at the top of the two columns refer to the definitions of Schmidt (1955) as follows n range (eye conditioned to neutral" white light) and u range (eye conditioned to coloured light Umstimmung)

In all subjects with deuteranomaly the quotient of anomaly (QA) based on the mid matching point (MP) was equal to or larger than 2.5 In subjects with protanomaly excluding two cases the QA was equal to or less than 0 72 One subject with protanomaly had a QA of 0 77 and the MR observed in his eye conditioned to the coloured light was nine scale units the end points of this range corresponding to QA 0 92 and 0 55 A relatively low perceived luminosity of the red light of the anomaloscope was observed in this subject who also passed the BK II pseudo isochromatic test without errors Similar liminal cases of protanomaly have been described earlier (Trendelenburg 1939 Gramberg Danielson and Schmidt, 1972 Heinsius 1975)

In another subject with protanomaly the end points of the MR were 0 and 59 (the eye conditioned to white light) and 0 and 73 (the eye conditoned to coloured light) In this subject too the luminosity of the red light of the anomaloscope appeared considerably lower than in normal subjects

In the series of 30 normal subjects the QA varied between 0 81 and 1 22 In no one case was the MR (the eye conditioned to white light) larger than three scal units In one normal subject the MR obtained in the eye conditioned to coloured light was 6 scale units larger than in the eye conditioned to white light. In one additional normal subject the corresponding difference was 5 scale units while it was 4 scale units or less in the other 28 normal subjects

Tables 3 4 and 5 as well as Figs. 5 6 7 8 9 and 10 illustrate several details of the results obtained with the F100 test at background luminance levels of 200 and 0 1 cd/m² In Figs 5 6 7 and 8 also the difference between the results obtained at these two luminance levels is shown The results presented in Tables

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RESULTS

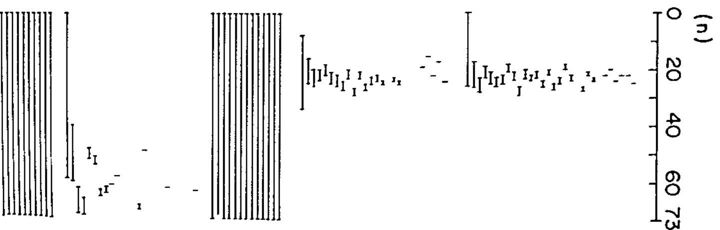
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N
P
EPA
PA
D
EDA
DA
(n)
0
20
40
60 73

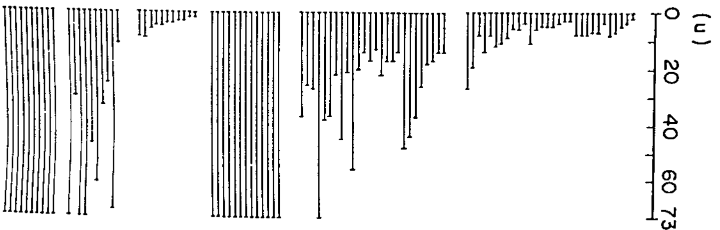

(u)
0
20
40
60 73

Fig 4

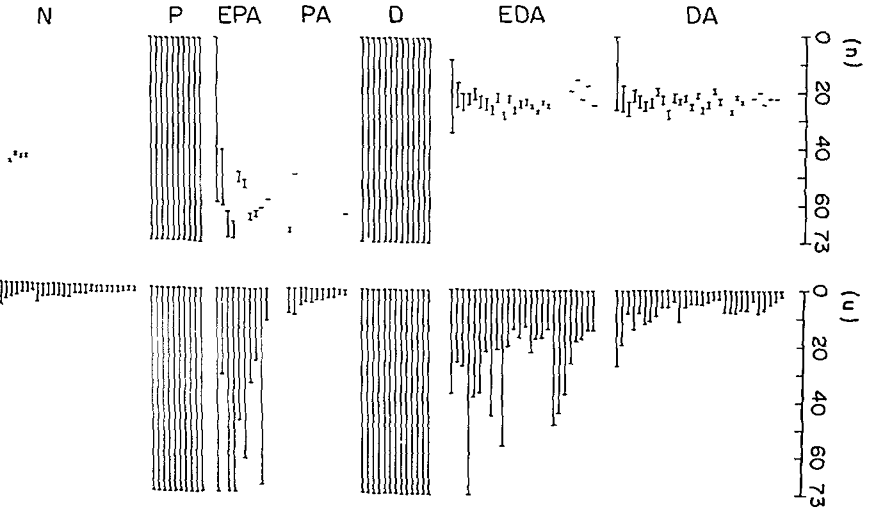
The distribution of the results obtained with the Nagel anomaloscope by subjects with deuteranomaly (30 cases DA) extreme deuteranomaly (26 cases, EDA), deuteranopia (13 cases D), protanomaly (11 cases PA), extreme protanomaly (10 cases, EPA), protanopia (10 cases, P) and normal subjects (30 cases N). The horizontal bars of the left column refer to the matching range (MR) obtained in the eye conditioned to white light (n), while the bars of the right column (displaced to start at the zero of the red green scale) refer to the matching range obtained in the eye conditioned to coloured light (u)

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3 4 and 5 are as follows mean error scores of quadrants I II III and IV (S_1 S_2 S_3 and S_4) mean error scores of opposite quadrants ($S_1 + S_3$) and ($S_2 + S_4$) mean total error score (ST) ratio between the mean error scores of pairs of opposite quadrants ($(S_1 + S_3)/(S_2 + S_4)$) and finally Y and PB which refer to the positions of the average maximum (number of cap) of errors in the yellow and blue purple hues respectively The mean and standard deviations obtained in 100 subjects with defective colour vision classified with the Nagel anomaloscope (Tables 3 and 4) and in 30 normal subjects (Table 5) are shown

It is evident from tables 3 and 4 that in subjects with all types of red green defects the average error scores of quadrants I and III obtained at 200 cd/m² background luminance are higher than the respective scores of quadrants II and IV and consequently $S_1 + S_3$ is larger than $S_2 + S_4$ The ratio $S_1 + S_3/S_2 + S_4$ is largest (8 2) in subjects with deuteranopia and smallest (1 8) in subjects with protanomaly The lowest $S_2 + S_4$ (21 8 ± 11 4) is found in subjects with deuteranopia and is almost as low as in normal subjects (17 4 ± 15 8 Table 5). The highest $S_2 + S_4$ (49 0 ± 20 8) is found in subjects with extreme protanomalia The highest total mean error score (ST) is found in subjects with deuteranopia (201 4 ± 34 7) followed by subjects with extreme protanomaly (160 0 ± 45 0) and protanopia (154 3 ± 53 9) The average values of Y are found at 15.5 to 16 0 (deutan types of defect) and 17 5 to 18 1 (protan types of defect) and the average values of PB are found at 57 6 to 58 0 and 58 0 to 59 9 respectively

Tables 3 and 4 also show that at low (0 1 cd/m²) background luminance level the error scores S_1 S_2 S_3 and S_4 are larger than those obtained at 200 cd/m² At both luminance levels the highest error score is found in quadrant III (S_3) In all types of red green defects the score $S_1 + S_3$ obtained at 0 1 cd/m² is larger than the score $S_2 + S_4$ but compared with the results obtained at 200 cd/m² the ratio $S_1 + S_3/S_2 + S_4$ is much smaller at 0 1 cd/m² varying between values 1 3 and 1 2 In normal subjects (0 1 cd/m² Table 5) the score $S_2 + S_4$ is larger than



N
P
EPA
PA
D
EDA
DA
(n)
0
20
40
60
73
(u)
0
20
40
60
73

Fig 4

The distribution of the results obtained with the Nagel anomaloscope by subjects with deuteranomaly (30 cases, DA), extreme deuteranomaly (26 cases, EDA), deuteranopia (13 cases D), protanomaly (11 cases, PA), extreme protanomaly (10 cases, EPA), protanopia (10 cases P) and normal subjects (30 cases N) The horizontal bars of the left column refer to the matching range (MR) obtained in the eye conditioned to white light (n) while the bars of the right column (displaced to start at the zero of the red green scale) refer to the matching range obtained in the eye conditioned to coloured light (u).

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3 4 and 5 are as follows mean error scores of quadrants I II III and IV (S_1 S_2 S_3 and S_4) mean error scores of opposite quadrants ($S_1 + S_3$) and ($S_2 + S_4$) mean total error score (ST) ratio between the mean error scores of pairs of opposite quadrants $(S_1 + S_3)/(S_2 + S_4)$ and finally Y and PB which refer to the positions of the average maximum (number of cap) of errors in the yellow and blue purple hues respectively The mean and standard deviations obtained in 100 subjects with defective colour vision classified with the Nagel anomaloscope (Tables 3 and 4) and in 30 normal subjects (Table 5) are shown

It is evident from tables 3 and 4 that in subjects with all types of red green defects the average error scores of quadrants I and III obtained at 200 cd/m² background luminance are higher than the respective scores of quadrants II and IV and consequently $S_1 + S_3$ is larger than $S_2 + S_4$ The ratio $S_4 + S_3/S_2 + S_4$ is largest (8 2) in subjects with deuteranopia and smallest (1 8) in subjects with *protanomaly* The lowest $S_2 + S_4$ (21 8 ± 11 4) is found in subjects with deuteranopia and is almost as low as in normal subjects (17 4 ± 15 8 Table 5) The highest $S_2 + S_4$ (49 0 ± 20 8) is found in subjects with extreme protanomalia The highest total mean error score (ST) is found in subjects with deuteranopia (201 4 ± 34 7) followed by subjects with extreme protanomaly (160 0 ± 45 0) and protanopia (154 3 ± 53 9) The average values of Y are found at 15 5 to 16 0 (deutan types of defect) and 17 5 to 18 1 (protan types of defect) and the average values of PB are found at 57 6 to 58 0 and 58 0 to 59 9 respectively

Tables 3 and 4 also show that at low (0 1 cd/m²) background luminance level the error scores S_1 S_2 S_3 and S_4 are larger than those obtained at 200 cd/m² At both luminance levels the highest error score is found in quadrant III (S_3) *In all* types of red green defects the score $S_1 + S_3$ obtained at 0 1 cd/m² is *larger than* the score $S_2 + S_4$ but compared with the results obtained at 200 cd/m² the ratio $S_1 + S_3/S_2 + S_4$ is much smaller at 0 1 cd/m² varying between values 1 3 and 1 2 In normal subjects (0 1 cd/m² Table 5) the score $S_2 + S_4$ *is larger than*

		S_1	S_2	S_3	S_4	S_1+S_3	S_2+S_4	ST	$\frac{S_1+S_3}{S_2+S_4}$	Y	PB
DA (n=30) 200 cd/m²	mean	32 4	15 7	55 6	15 7	88 0	31 4	119 4	2 8	15 5	58 0
	S D	24 0	10 3	39 7	13 7	60 2	22 2	72 0			
0 1 cd/m²	mean	142 4	123 0	171 0	128 4	313 3	251 4	564 8	1 2	12 9	55 3
	S D	58 5	45 5	56 0	42 4	102 3	76 0	170 4			
difference 0 1–200 cd/m²	mean	110 0	107 4	115 4	112 7	225 3	220 1	445 4	1 0	12 3	54 4
	S D	48 9	42 7	52 2	42 5	80 1	71 6	140 6			
EDA (n=26) 200 cd/m²	mean	43 7	19 4	65 0	18 7	108 6	38 2	146 8	2 8	15 7	57 6
	S D	23 9	11 8	34 5	13 2	53 3	19 5	66 0			
0 1 cd/m²	mean	175 6	130 4	180 9	137 6	356 5	268 1	624 5	1 3	12 9	55 0
	S D	49 9	41 3	43 6	41 0	75 4	68 5	137 2			
difference 0 1–200 cd/m²	mean	131 9	111 0	115 9	118 9	247 8	229 9	477 8	1 1	12 3	54 0
	S D	51 2	41 9	47 4	36 9	72 6	63 7	120 4			
D (n=13) 200 cd/m²	mean	78 8	11 5	100 7	10 4	179 5	21 8	201 4	8 2	16 0	57 8
	S D	23 4	9 3	13 6	5 1	27 6	11 4	34 7			
0 1 cd/m²	mean	186 8	142 8	202 0	150 9	388 8	293 8	682 5	1 3	12 3	54 6
	S D	51 2	39 2	36 9	46 2	75 8	77 9	147 0			
difference 0 1–200 cd/m²	mean	107 9	131 4	101 3	140 5	209 2	271 9	481 1	0 8	11 0	53 0
	S D	56 4	39 5	42 7	47 5	80 8	78 1	151 7			

TABLE 3

		S	S_3	S_5	S	S S_8	S S_4	ST	$\frac{S_1+S}{S_3+S}$	Y	PB
PA (n 11) ?00 cd m	mean	5 1	18 1	3‥0	13 6	57 1	31 7	88 8	1 8	18 1	58 0
	S D	19 2	14 0	5 6	10 5	41 9	0 3	53 9			
0 1 cd m²	mean	127 6	116 1	157 6	109 1	85 3	?5 2	510 5	1 3	14 2	56 5
	S D	58 1	47 6	5‥1	44 6	99 1	86 5	177 8			
d fference 0 1 00 cd m	mean	10?5	98 0	1 5 6	95 5	2 8 2	193 5	421 6	1 2	13 5	56 2
	S D	45 3	38 8	54 0	4? 8	82 ‥	76 9	146 8			
I PA (n = 10) ?00 cd m²	mean	42 7	23 6	72 3	5 4	115 0	49 0	160 0	3	17 5	59 9
	S D	16 3	12 3	21 2	12 1	8 7	0 8	45 0			
0 1 cd m²	mean	147 0	140 8	190 3	144 1	337 3	284 9	622 2	1 2	15 1	57 4
	S D	33 5	37 3	33 9	21 1	42 0	48 6	83 6			
d fference 0 1– 00 cd/m²	mean	104 3	117 2	118 0	118 7	22? 3	235 9	458 2	0 9	14 5	56 3
	S D	37 6	35 4	41 5	?4 9	37 8	44 9	71 2			
P (n = 10) 00 cd/m²	mean	50 0	23 9	58 3	22 1	108 3	46 0	154 3	2 4	18 0	59 8
	S D	25 7	11 2	18 4	13 3	39 9	19 6	53 9			
0 1 cd/m²	mean	143 3	123 7	152 4	125 8	295 7	249 5	545 2	1 2	14 1	56 7
	S D	43 4	42 9	38 2	21 9	73 1	57 5	125 8			
d fference 0 1– 00 cd/m²	mean	93 3	99 8	94 1	103 7	187 4	?03 5	390 9	0 9	12 9	55 1
	S D	60 2	46 3	51 6	24 8	100 5	63 8	160 5			

TABLF 4

			S_1	S_2	S_3	S_4	S_1+S_3	S_2+S_4	ST	$\frac{S_1+S_3}{S_2+S_4}$	Y	PB
DA (n=30)	200 cd/m²	mean	32 4	15 7	55 6	15 7	88 0	31 4	119 4	2 8	15 5	58 0
		S D	24 0	10 3	39 7	13 7	60 2	22 2	72 0			
	0 1 cd/m²	mean	142 4	123 0	171 0	128 4	313 3	251 4	564 8	1 2	12 9	55 3
		S D	58 5	45 5	56 0	42 4	102 3	76 0	170 4			
	difference 0 1–200 cd/m²	mean	110 0	107 4	115 4	112 7	225 3	220 1	445 4	1 0	12 3	54 4
		S D	48 9	42 7	52 2	42 5	80 1	71 6	140 6			
EDA (n=26)	200 cd/m²	mean	43 7	19 4	65 0	18 7	108 6	38 2	146 8	2 8	15 7	57 6
		S D	23 9	11 8	34 5	13 2	53 3	19 5	66 0			
	0 1 cd/m²	mean	175 6	130 4	180 9	137 6	356 5	268 1	624 5	1 3	12 9	55 0
		S D	49 9	41 3	43 6	41 0	75 4	68 5	137 2			
	difference 0 1–200 cd/m²	mean	131 9	111 0	115 9	118 9	247 8	229 9	477 8	1 1	12 3	54 0
		S D	51 2	41 9	47 4	36 9	72 6	63 7	120 4			
D (n=13)	200 cd/m²	mean	78 8	11 5	100 7	10 4	179 5	21 8	201 4	8 2	16 0	57 8
		S D	23 4	9 3	13 6	5 1	27 6	11 4	34 7			
	0 1 cd/m²	mean	186 8	142 8	202 0	150 9	388 8	293 8	682 5	1 3	12 3	54 6
		S D	51 2	39 2	36 9	46 2	75 8	77 9	147 0			
	difference 0 1–200 cd/m²	mean	107 9	131 4	101 3	140 5	209 2	271 9	481 1	0 8	11 0	53 0
		S D	56 4	39 5	42 7	47 5	80 8	78 1	151 7			

TABLE 3

		S	S	S	S	S S	S S	ST	S_L+S_3 / S_1+S	Y	PB
PA (n 11) 900 cd m	mean	5 1	18 1	3 0	13 6	57 1	31 7	89 8	1 8	18.1	58 0
	S D	19	14 0	25 6	10 5	41 9	0 3	53 9			
0 1 cd m	mean	127 6	116 2	157 6	109 1	95 3	7 5	510.5	1 3	14 2	56 5
	S D	58 1	47 6	5 1	44 6	99 1	86 5	177 8			
difference 0 1 00 cd m²	mean	102 5	98 0	125 6	95 5	8 2	193 5	4 16	1 2	13 5	56
	S D	45 3	38 8	54 0	42 8	82 2	76 9	146 8			
FPA (n 10) 900 cd m	mean	42 7	23 6	72 3	5 4	115 0	49 0	160 0	2 3	17 5	59 9
	S D	16 3	12 3	21 2	12 1	8 7	0 8	45 0			
0 1 cd m²	mean	147 0	140 8	190 3	144 1	337 3	84 9	622 2	1 2	15 1	57 4
	S D	33 5	37 3	33 9	21 1	42 0	48 6	83 6			
difference 0 1– 00 cd m²	mean	104 3	117 2	118 0	118 7	222.3	235 9	458 2	0 9	14 5	56 3
	S D	37 6	35 4	41 5	24 9	37 8	44 9	71 2			
P (n=10) 00 cd/m²	mean	50 0	73 9	58 3	22 1	108 3	46 0	354 3	2 4	18 0	59 8
	S D	5 7	11 2	18 4	13 3	39 9	19 6	53 9			
0 1 cd/m²	mean	143 3	123 7	152 4	125 8	295 7	249 5	545 2	1 2	14 1	56 7
	S D	43 4	42 9	38 2	21 9	73 1	57 5	175 8			
difference 0 1– 00 cd/m²	mean	93 3	99 8	94 1	103 7	187 4	03 5	390 9	0 9	12 9	55 1
	S D	60 2	46 3	51 6	24 8	100 5	63 8	160 5			

TABLE 4

		S_1	S_2	S_3	S_4	S_1+S_3	S_2+S_4	ST	$\frac{S_1+S_3}{S_2+S_4}$	Y	PB
N (n=30)	mean	6 1	11 7	7 0	5 8	13 1	17 4	30 6	—	—	—
200 cd/m²	S D	5 0	10 2	6 5	7 2	9 9	15 8	23 8			
	mean	43 1	69 7	65 9	60 3	109 0	130 0	239 0	0 8	3 5	48 5
0 1 cd/m²	S D	21 0	26 4	21 4	23 5	35 5	44 5	75 4			
difference	mean	37 0	58 0	58 8	54 5	95 8	112 5	208 4	0 9	3 5	48 5
0 1–200 cd/m²	S D	19 3	22 2	19 5	21 5	30 9	37 0	61 5			

TABLE 5

Tables 3 4 and 5

Results obtained in the Farnsworth Munsell 100 hue test (F100) by subjects with deuteranomaly (30 cases DA) extreme deuteranomaly (26 cases EDA) deuteranopia (13 cases D) protanomaly (11 cases PA) extreme protanomaly (10 cases EPA) protanopia (10 cases P) and normal subjects (30 cases N) Results obtained at background luminosity levels of 200 and 0 1 cd/m² are shown as well as the difference between the mean error scores obtained at 0 1 and 200 cd/m² For details see text

$S_1 + S_2$ and the ratio $S_1 + S_3/S_2 + S_4$ is 0 8 The largest total mean error score (ST) obtained at 0 1 cd/m² luminance is found in subjects with deuteranopia (682 5 ± 147 0) followed by those with extreme deuteranomaly (624 5 ± 137 2) and by those with extreme protanomaly (622 2 ± 83 6) At 0 1 cd/m² the average values of Y are found at 12 3 to 12 9 (deutan types of defect) and at 14 1 to 15 1 (protan types of defect) and the average values of PB are found at 54 6 to 55 3 and 56 5 to 57 4 respectively Apparently reduced illumination has displaced the error maxima in the yellow (Y) of the subjects with defective colour vision towards red hues and the error maxima in the blue purple (PB) towards blue hues

Also the difference between the results obtained at 0 1 and 200 cd/m² luminance levels is given in Tables 3 and 4 (subjects with red green defects) and Table 5 (normal subjects) The largest difference in the mean error score is found in quadrant IV (140 0 ± 47.5) in subjects with deuteranopia in quadrant I (131 9 ± 51 2) in those with extreme deuteranomaly in quadrant III (125 6 ± 54 0) in those with protanomaly in quadrant IV (118 7 ± 24 9) in those with extreme protanomaly in quadrant III (115 4 ± 52 2) in those with deuteranomaly and in quadrant IV (103 7 ± 24 8) in those with *protanopia. In normal subjects* an almost equal difference in the mean error score (obtained at 0 1 and 200 cd/m²) is found in quadrant III (58 8 ± 19 5) and in quadrant II (58 0 ± 22 2) In subjects with deuteranomaly extreme deuteranomaly and protanomaly the difference in $S_1 + S_3$ was larger than in $S_2 + S_4$ *while the differen e* in $S_2 + S_4$ was larger in subjects with deuteranopia protanopia and extreme protanomaly In all types of red green defects the difference between the results obtained at 0 1 and 200 cd/m² shows that the average maxima of the mean error score (Y and PB) compared with separate results *obtained* at 0 1 and 200 cd/m² are somewhat further displaced towards red hues (Y), and towards blue hues (PB)

The diagrams of Figs 5 6 7 and 8 illustrate the distribution of the *mean error* scores obtained in the Farnsworth Munsell 100 hue test by subjects with deuteranomaly (30 cases DA), extreme deuteranomaly (26 cases, EDA) deuteranopia (13 cases, D) protanomaly (11 cases PA) extreme protanomaly (10 cases EPA) protanopia (10 cases P) and *normal* subjects (30 cases N) Results obtained at background luminosity levels of 200 cd/m² (to left) and 0 1 cd m² (center) are shown as well as the difference (d) between the mean error scores obtained at 0 1 and 200 cd/m² (to right). The inner and outer broken solid lines show the mean score and the mean score + standard deviation respectively The interrupted lines of Figs 6 and 7 (diagrams of the dichromats D200 and P 00) indicate the limits of the quad ants I II III and IV

		S_1	S_2	S_3	S_4	S_1+S_3	S_2+S_4	ST	$\frac{S_1+S_3}{S_2+S_4}$	Y	PB
N (n=30)	mean	6 1	11 7	7 0	5 8	13 1	17 4	30 6	–	–	–
200 cd/m²	S D	5 0	10 2	6 5	7 2	9 9	15 8	23 8			
	mean	43 1	69 7	65 9	60 3	109 0	130 0	239 0	0 8	3 5	48 5
0 1 cd/m²	S D	21 0	26 4	21 4	23 5	35 5	44 5	75 4			
difference	mean	37 0	58 0	58 8	54 5	95 8	112 5	208 4	0 9	3 5	48 5
0 1–200 cd/m²	S D	19 3	22 2	19 5	21 5	30 9	37 0	61 5			

TABLE 5

Tables 3 4 and 5

Results obtained in the Farnsworth Munsell 100 hue test (F100) by subjects with deuteranomaly (30 cases DA) extreme deuteranomaly (26 cases EDA) deuteranopia (13 cases D) protanomaly (11 cases PA) extreme protanomaly (10 cases EPA) protanopia (10 cases P) and normal subjects (30 cases N) Results obtained at background luminosity levels of 200 and 0 1 cd/m² are shown as well as the difference between the mean error scores obtained at 0 1 and 200 cd/m² For details see text

$S_1 + S_3$ and the ratio $S_1 + S_3/S_2 + S_4$ is 0 8 The largest total mean error score (ST) obtained at 0 1 cd/m² luminance is found in subjects with deuteranopia (682 5 ± 147 0) followed by those with extreme deuteranomaly (624 5 ± 137 2) and by those with extreme protanomaly (622 2 ± 83 6) At 0 1 cd/m² the average values of Y are found at 12 3 to 12 9 (deutan types of defect) and at 14 1 to 15 1 (protan types of defect) and the average values of PB are found at 54 6 to 55 3 and 56 5 to 57 4 respectively Apparently reduced illumination has displaced the error maxima in the yellow (Y) of the subjects with defective colour vision towards red hues and the error maxima in the blue purple (PB) towards blue hues

Also the difference between the results obtained at 0 1 and 200 cd/m² luminance levels is given in Tables 3 and 4 (subjects with red green defects) and Table 5 (normal subjects) The largest difference in the mean error score is found *in quadrant IV* (140 0 ± 47 5) in subjects with deuteranopia in quadrant I (131 9 ± 51 2) in those with extreme deuteranomaly in quadrant III (125 6 ± 54 0) in those with protanomaly in quadrant IV (118 7 ± 24 9) in those with extreme protanomaly in quadrant III (115 4 ± 52 2) in those with deuteranomaly and in quadrant IV (103 7 ± 24 8) in those with protanopia In *normal subjects* an almost equal difference in the mean error score (obtained at 0 1 and 200 cd/m²) is found in quadrant III (58 8 ± 19 5) and in quadrant II (58 0 ± 22 2) In subjects with deuteranomaly extreme *deuteranomaly and protanomaly* the difference in $S_1 + S_3$ was larger than in $S_2 + S_4$ while the difference in $S_2 + S_4$ was larger in subjects with deuteranopia protanopia, and extreme protanomaly In all types of red green defects the difference between the results obtained at 0 1 and 200 cd/m² shows that the average maxima of the mean error score (Y and PB) compared with separate results obtained at 0 1 and 200 cd/m² are somewhat further displaced towards red hues (Y) and towards blue hues (PB)

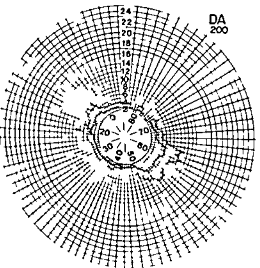
The diagrams of Figs 5 6 7 and 8 illustrate the distribution of the mean error scores obtained in the Farnsworth Munsell 100 hue test by subjects with deuteranomaly (20 cases DA) extreme deuteranomaly (26 cases EDA) deuteranopia (13 cases D), protanomaly (11 cases PA) extreme protanomaly (10 cases EPA) protanopia (10 cases P) and normal subjects (30 cases N) Results obtained at background luminosity levels of 200 cd/m² (to left) and 0 1 cd m² (center) are shown as well as the difference (d) between the mean error scores obtained at 0 1 and 200 cd/m² (to right). The inner and outer broken solid lines show the mean score and the mean score + standard deviation respectively The interrupted lines of Figs. 6 and 7 (diagrams of the dichromats D200 and P200) indicate the limits of the quadrants I II III and IV

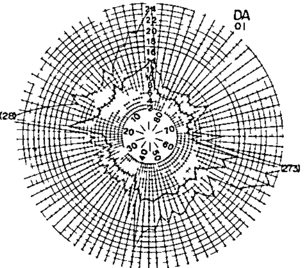
		S_1	S_2	S_3	S_4	S_1+S_3	S_2+S_4	ST	$\frac{S_1+S_3}{S_2+S_4}$	Y	PB
N (n=30) 200 cd/m²	mean	6 1	11 7	7 0	5 8	13 1	17 4	30 6	—	—	—
	S D	5 0	10 2	6 5	7 2	9 9	15 8	23 8			
0 1 cd/m²	mean	43 1	69 7	65 9	60 3	109 0	130 0	239 0	0 8	3 5	48 5
	S D	21 0	26 4	21 4	23 5	35 5	44 5	75 4			
difference 0 1–200 cd/m²	mean	37 0	58 0	58 8	54 5	95 8	112 5	208 4	0 9	3 5	48 5
	S D	19 3	22 2	19 5	21 5	30 9	37 0	61 5			

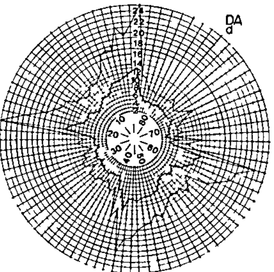
TABLE 5

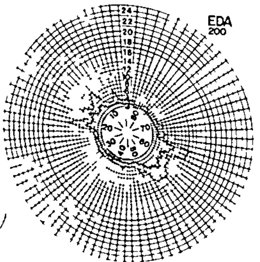
Tables 3 4 and 5

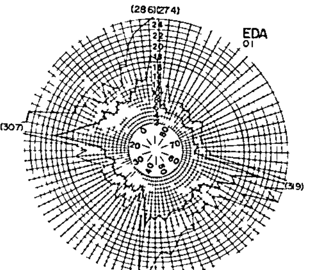
Results obtained in the Farnsworth Munsell 100 hue test (F100) by subjects with deuteranomaly (30 cases DA) extreme deuteranomaly (26 cases EDA) deuteranopia (13 cases D) protanomaly (11 cases PA) extreme protanomaly (10 cases EPA) protanopia (10 cases P) and normal subjects (30 cases N) Results obtained at background luminosity levels of 200 and 0 1 cd/m² are shown as well as the difference between the mean error scores obtained at 0 1 and 200 cd/m² For details see text

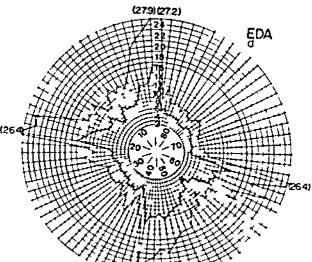

DA
200

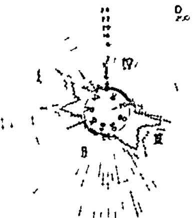

DA
01
(28)
(273)

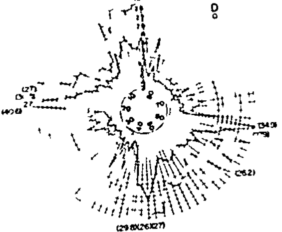

DA
d

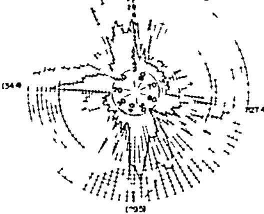

EDA
200

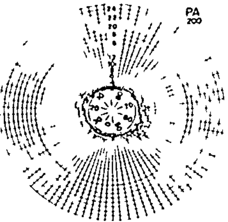

EDA
01
(286)(274)
(307)
(319)

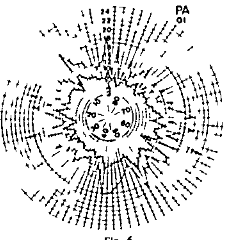

EDA
d
(279)(272)
(264)
(264)











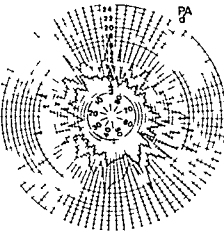
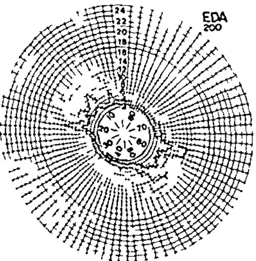
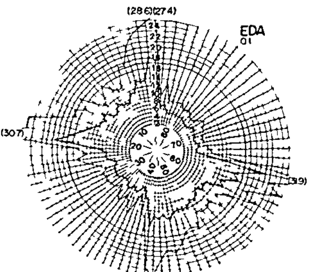
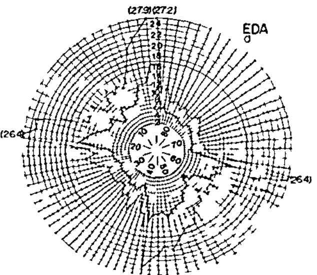
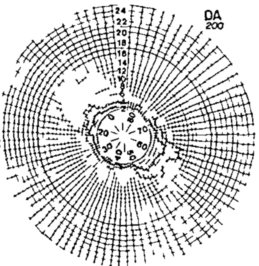


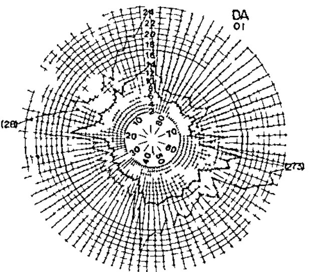
Fig. 6


DA
200


DA
01
(28)
(273)


DA
d


EDA
200


EDA
01
(286)(274)
(307)
(319)

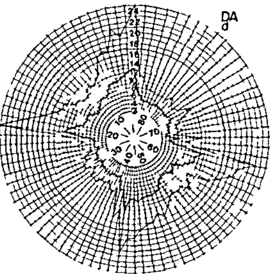
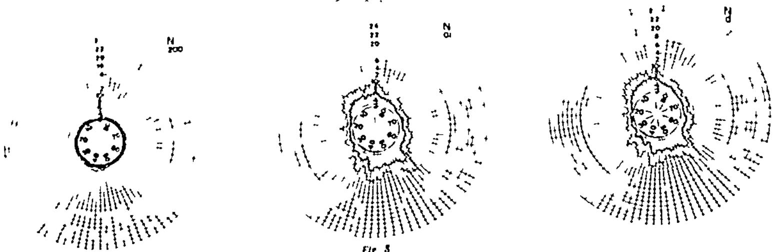
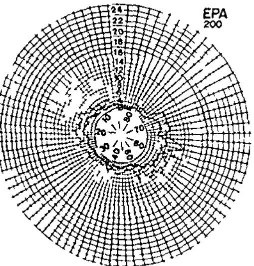

EDA
d
(279)(272)
(264)
(264)

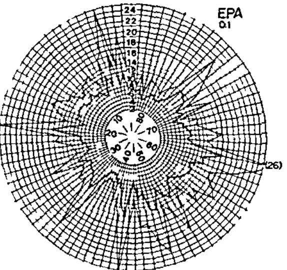
Fig 3

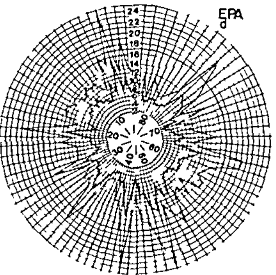


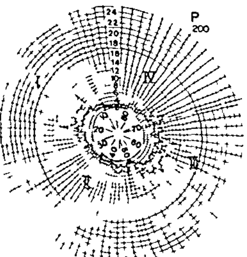
Figs 5 6 7 and 8

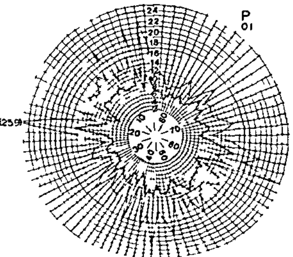
Diagrams showing the di tributions of the mean error scores obtained in the Farnsworth Munsell 100 hue test (F100) by subjects with protanomaly (11 cases, PA), extreme deuteranomaly (30 cases, DA), extreme deuteranomaly (26 cases, EDA), deuteranopia (13 cases D) protanomaly (10 cases FPA), protanopia (10 cases, P) and normal subjects (30 cases N). Results obtained at background *luminosity* levels of 00 cd/m² (to left) and 0 1 cd/m² (center) are shown as well as the difference (d) between the mean error scores obtained at 0 1 and 00 cd/m² (to right). The inner and outer broken solid lines show the mean score and the mean score + standard deviation respectively The interrupted lines of Figs. 6 and 7 (diagrams of the d chromats D 00 and P 00) indicate the limits of the quadrants I II III and IV (see methods)

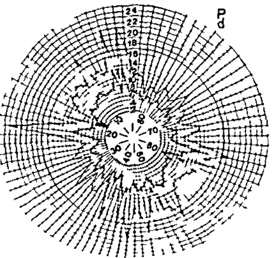

EPA
200
24 22 20 18 16 14 12 10
10 20 30 40 50 60 70 80


EPA
0.1
24 22 20 18 16 14
10 20 30 40 50 60 70 80
(26)


EPA
d
24 22 20 18 16 14
10 20 30 40 50 60 70 80


P
200
24 22 20 18 16 14 12 10
10 20 30 40 50 60 70 80
I II III IV


P
01
24 22 20 18 16 14
10 20 30 40 50 60 70 80
(25.9)


P
d
24 22 20 18 16 14
10 20 30 40 50 60 70 80

luminance of both pairs of quadrants $S_1 + S_3$ and $S_2 + S_4$ of the F100 test are statistically compared (Student s t test) with the corresponding difference found in the series of normal subjects In all subjects with different types of red green defects the increase in the mean error score $S_1 + S_3$ (P value < 0.05) and $S_2 + S_4$ ($P < 0.01$) is significantly higher than in normal subjects Also the increase in the total mean error score (ST) is significantly higher in all subjects with different types of red green defects ($P < 0.01$) compared with the series of normal subjects The increase in the ST is almost equally large in all the different groups of red green defects Only the increase in the ST of subjects with extreme deuteranomaly (477 8 ± 120 4) is statistically suggestively higher ($P = 0.086$) compared with the increase in the ST (390 9 ± 160 5) observed in subjects with protanopia

Figs 9 and 10 illustrate the results obtained by individual subjects in the F100 test performed at background luminosity levels of 200 and 0 1 cd/m² Evidently in all types of red green defects the results of Fig 9 are distributed over a much larger range of error scores (ST) at 0 1 cd/m² compared with the results obtained at 200 cd/m² and there is considerable variation in the slope of the lines related to the individual results Fig 10 on the other hand illustrates the fact in all types of red green defects the ratio $S_1 + S_3/S_2 + S_4$ (individual results) in many cases is lower at a background luminosity level of 0 1 cd/m² than the same ratio at 200 cd/m² In this illustration the black symbols refer to the luminance level 0 1 cd/m² and the white symbols to 200 cd/m² The interrupted line and the solid line refer to the limits of the results obtained by normal subjects at 0 1 and 200 cd/m² respectively

Results obtained with the colour caps of the separate first box of the F100 test (caps numbered 85 to 21) are illustrated in Figs 11 12 and 13 Fig 11 illustrates the mean error scores of the caps of the first box (SB_1) obtained at five different background luminance levels (200 10 1 0 1 and 0 02 cd/m²) The mean error score and standard deviation obtained in the different types of red green defects and in a series of normal subjects are shown In all groups with different types of red green defects as well as in normal subjects, there is a slight increase in the mean error score when the luminance level is decreased from 10 cd/m² to 1 cd m and there is a large increase in the mean error score at luminance levels lower than 0 1 cd/m² A statistical analysis of these results (Student s t test) showed that in 10 subjects with deuteranomaly the difference between the mean error scores (SB_1) obtained at 200 cd/m² (31 2 ± 23.5) and at 10 cd/m² (37 0 ± 9 0) is statistically suggestive ($P = 0.055$) while in other groups of red green defective subjects and in 30 normal subjects, the corresponding difference in the SB_1 is not statistically significant ($P > 0.1$) At 1 0 cd/m² the SB_1 compared

These diagrams very clearly illustrate the increase as well as the alteration in the distribution of the error scores of all types of subjects with red green defects caused by the reduction of illumination An increase in the error scores typical of both the red green and tritan types of defects is quite evident in all groups of subjects with red green defects and is particularly important in subjects with deutan types of the defect Interestingly the error score indicating a tritan type of the defect has markedly increased in subjects with all types of red green defects and clearly exceeds the physiological tritan type of the defect typical of normal subjects (Fig 8) at mesopic illuminations

Table 6 shows the results of the statistical analysis of some of the results already illustrated in Tables 3 4 and 5 and in Figs 5 6 7 and 8 In Table 6 the difference between the mean error scores obtained at 0 1 and 200 cd/m²

		S_1+S_3 difference		S_2+S_4 difference	
N (n=30)	mean S D	95 8 30 9	P value	112 5 37 0	P value
DA (n-30)	mean S D	225 3 80 1	< 0 001	220 1 71 6	< 0 001
EDA (n -26)	mean S D	247 8 72 6	< 0 001	229 9 63 7	< 0 001
D (n=13)	mean S D	209 2 80 8	< 0 001	271 9 78 1	< 0 001
PA (n=11)	mean S D	228 2 82 2	< 0 001	193 5 76 9	0 006
EPA (n=10)	mean S D	222 3 37 8	< 0 001	235 9 44 9	< 0 001
P (n=10)	mean S D	187 4 100 5	0 018	203 5 63 8	0 001

Table 6

Statistical analysis of the differences between the mean error scores obtained in the Farnsworth Munsell 100 hue test (F100) at background luminance levels of 0 1 and 200 cd/m² Results of pairs of opposite quadrants $S_1 + S_3$ and $S_2 + S_4$ *(mean error score of the difference 0 1 – 200 cd/m²)* obtained by different groups of subjects with defective colour vision (classified with the Nagel anomaloscope) are statistically compared with the respective results obtained in a series of normal subjects Also the P value of the Student s t test is shown

luminance of both pairs of quandrants $S_1 + S_3$ and $S_2 + S_4$ of the F100 test are statistically compared (Student s t test) with the corresponding difference found in the series of normal subjects In all subjects with different types of red green defects the increase in the mean error score $S_1 + S_3$ (P value < 0.05) and $S_2 + S_4$ ($P < 0.01$) is significantly higher than in normal subjects Also the increase in the total mean error score (ST) is significantly higher in all subjects with different types of red green defects ($P < 0.01$) compared with the series of normal subjects The increase in the ST is almost equally large in all the different groups of red green defects Only the increase in the ST of subjects with extreme deuteranomaly (477 8 ± 120 4) is statistically suggestively higher ($P = 0.086$) compared with the increase in the ST (390 9 ± 160.5) observed in subjects with protanopia

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Results obtained with the colour caps of the separate first box of the F100 test (caps numbered 85 to 21) are illustrated in Figs 11 12 and 13 *Fig 11 illustrates* the mean error scores of the caps of the first box (SB_1) obtained at five different background luminance levels (200 10 1 0 1 and 0 02 cd/m²). The mean error score and standard deviation obtained in the different types of red green defects and in a series of normal subjects are shown In all groups with different types of red green defects as well as in normal subjects there is a *slight increase in the* mean error score when the luminance level is decreased from 10 cd/m² to 1 cd m² and there is a large increase in the mean error score at luminance levels lower than 0 1 cd/m² A statistical analysis *of these* results (Student s t test) showed that in 30 subjects with deuteranomaly the difference between *the mean* error scores (SB_1) obtained at 200 cd/m² (31.2 ± 23.5) and at 10 cd/m² (37 0 ± 29 0) is statistically suggestive ($P = 0.055$) while in other groups of red green defective subjects and in 30 normal subjects, the corresponding difference in the SB_1 is not statistically significant ($P > 0.1$). At 1 0 cd/m² the SB_1 compared

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Table 6 shows the results of the statistical analysis of some of the results already illustrated in Tables 3, 4 and 5 and in Figs 5, 6, 7 and 8 In Table 6 the difference between the mean error scores obtained at 0 1 and 200 cd/m^2

		S_1+S_3 difference		S_2+S_4 difference	
N (n=30)	mean S D	95 8 30 9	P value	112 5 37 0	P value
DA (n=30)	mean S D	225 3 80 1	< 0 001	220 1 71 6	< 0 001
EDA (n =26)	mean S D	247 8 72 6	< 0 001	229 9 63 7	< 0 001
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Table 6

Statistical analysis of the differences between the mean error scores obtained in the Farnsworth Munsell 100 hue test (F100) at background luminance levels of 0 1 and 200 cd/m^2 Results of pairs of opposite quadrants $S_1 + S_3$ and $S_2 + S_4$ (mean error score of the difference 0 1–200 cd/m^2) obtained by different groups of subjects with defective colour vision (classified with the Nagel anomaloscope) are statistically compared with the respective results obtained in a series of normal subjects Also the P value of the Student s t test is shown

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Figs 9 and 10 illustrate the results obtained by individual subjects in the F100 test performed at background luminosity levels of 200 and 0 1 cd/m² Evidently in all types of red green defects the results of Fig 9 are distributed over a much larger range of error scores (ST) at 0 1 cd/m² compared with the results obtained at 200 cd/m² and there is considerable variation in the slope of the lines related to the individual results Fig 10 on the other hand illustrates the fact in all types of red green defects the ratio $S_1 + S_3/S_2 + S_4$ (individual results) in many cases is lower at a background luminosity level of 0 1 cd/m² than the same ratio at 200 cd/m² In this illustration the black symbols refer to the luminance level 0 1 cd/m² and the white symbols to 200 cd/m² The interrupted line and the solid line refer to the limits of the results obtained by normal subjects at 0 1 and 200 cd/m² respectively

Results obtained with the colour caps of the separate first box of the F100 test (caps numbered 85 to 21) are illustrated in Figs 11 12 and 13 Fig 11 illustrates the mean error scores of the caps of the first box (SB_1) obtained at *five different* background luminance levels (200 10 1 0 1 and 0 02 cd/m²) The mean error score and standard deviation obtained in the different types of red green defects and in a series of normal subjects are shown In all groups with different types of red green defects as well as in normal subjects there is a slight increase in the mean error score when the luminance level is decreased from 10 cd/m² to 1 cd/m² and there is a large *increase in* the mean error score at luminance levels lower than 0 1 cd/m² A statistical analysis of these results (Student s t test) showed that in 30 subjects with deuteranomaly the *difference* between the mean error scores (SB_1) obtained at 200 cd/m² (31 2 ± 23 5) and at 10 cd/m² (37 0 ± 29 0) is statistically suggestive ($P = 0\,055$) while in other groups of red green defective subjects and in 30 normal subjects the corresponding difference *in the* SB_1 is not statistically significant ($P > 0\,1$). At 1 0 cd/m² the SB_1 compared

These diagrams very clearly illustrate the increase, as well as the alteration in the distribution of the error scores of all types of subjects with red green defects caused by the reduction of illumination An increase in the error scores typical of both the red green and tritan types of defects is quite evident in all groups of subjects with red green defects and is particularly important in subjects with deutan types of the defect Interestingly the error score indicating a tritan type of the defect has markedly increased in subjects with all types of red green defects and clearly exceeds the physiological tritan type of the defect typical of normal subjects (Fig 8) at mesopic illuminations

Table 6 shows the results of the statistical analysis of some of the results already illustrated in Tables 3, 4 and 5 and in Figs 5 6, 7 and 8 In Table 6 the difference between the mean error scores obtained at 0 1 and 200 cd/m²

		S_1+S_3 difference		S_2+S_4 difference	
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Table 6

Statistical analysis of the differences between the mean error scores obtained in the Farnsworth Munsell 100 hue test (F100) at background luminance levels of 0 1 and 200 cd/m² Results of pairs of opposite quadrants $S_1 + S_3$ and $S_2 + S_4$ (mean error score of the difference 0 1–200 cd/m²) obtained by different groups of subjects with defective colour vision (classified with the Nagel anomaloscope) are statistically compared with the respective results obtained in a series of normal subjects Also the P value of the Student s t test is shown

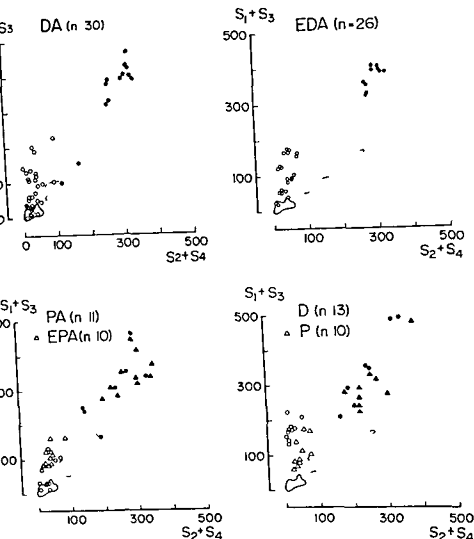


Fig 10

Correlation between the scores $S_1 + S$ and $S_2 + S_4$ obtained in the Farnsworth Munsell 100-hue test (F100) at background luminosity levels of ᵓ00 cd/m (circles and white triangles) and 0 1 cd/m² (black dots and black triangles). $S + S_3$ and $S_2 + S_4$ refer to the mean error scores of the pairs of quadrants I III and II IV of the F100 test (see methods) Results obtained in subjects with defect ve colour vision (classified with the Nagel anomaloscope) are shown The limits of the solid line (200 cd/m²) and of the interrupted line (0 1 cd/m²) ind cate the distribution of the results obtained by normal subjects.

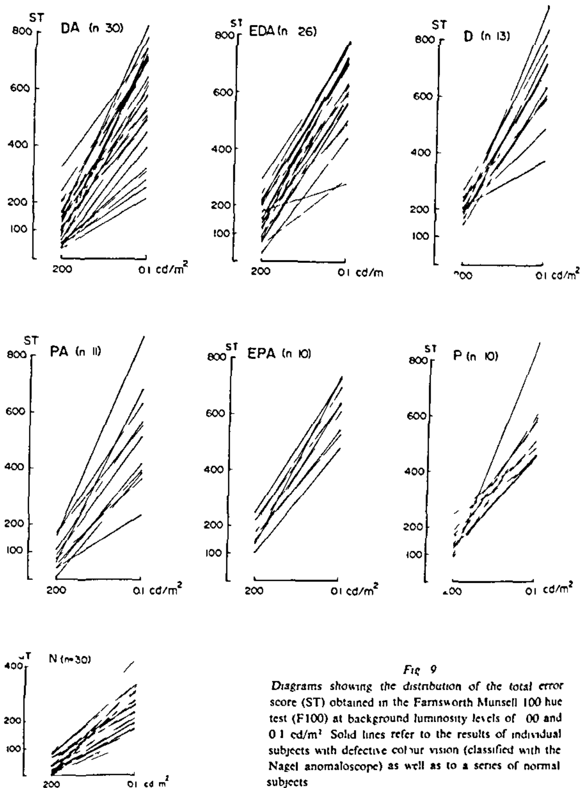


Fig 9

Diagrams showing the distribution of the total error score (ST) obtained in the Farnsworth Munsell 100 hue test (F100) at background luminosity levels of 00 and 0 1 cd/m² Solid lines refer to the results of individual subjects with defective colour vision (classified with the Nagel anomaloscope) as well as to a series of normal subjects

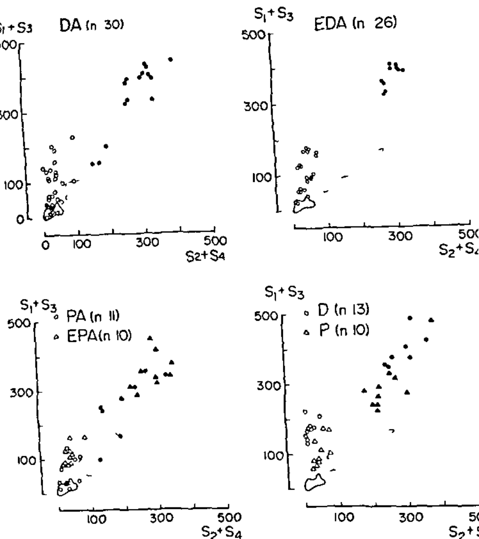


Fig 10

Correlation between the scores $S_1 + S_3$ and $S_2 + S_4$ obtained in the Farnsworth Munsell 100-hue test (F100) at background luminosity levels of 200 cd/m² (circles and white triangles) and 0 1 cd/m² (black dots and black triangles). $S_1 + S_3$ and $S_2 + S_4$ refer to the mean error scores of the pa rs of quadrants I III and II IV of the F100 test (see methods). Results obtained in subjects with defective colour vision (classified with the Nagel anomaloscope) are shown The limits of the solid line (200 cd/m²) and of the interrupted line (0 1 cd/m²) indicate the distribution of the results obta ned by normal subjects.

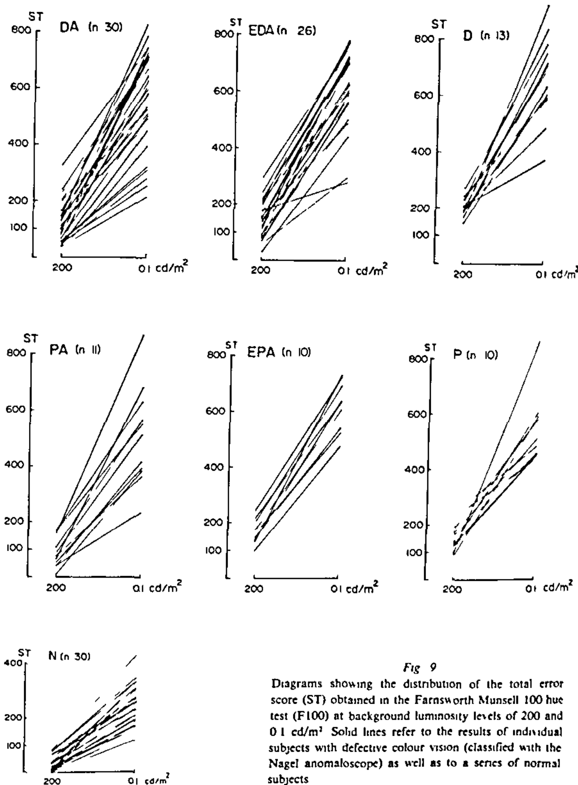


Fig 9

Diagrams showing the distribution of the total error score (ST) obtained in the Farnsworth Munsell 100 hue test (F100) at background luminosity levels of 200 and 0 1 cd/m² Solid lines refer to the results of individual subjects with defective colour vision (classified with the Nagel anomaloscope) as well as to a series of normal subjects

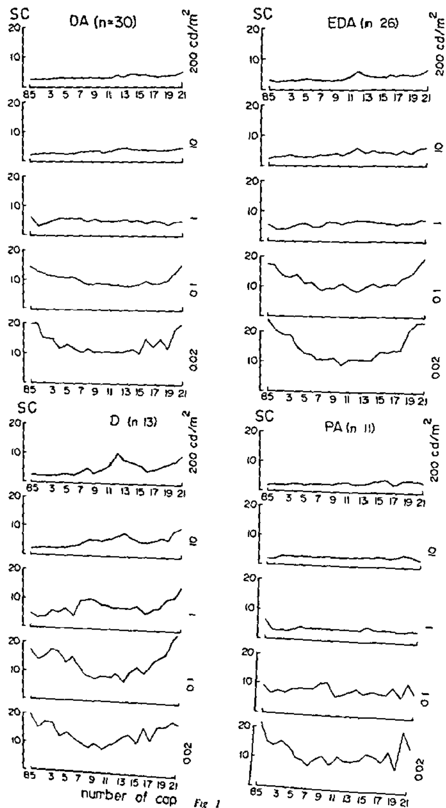


Fig 1

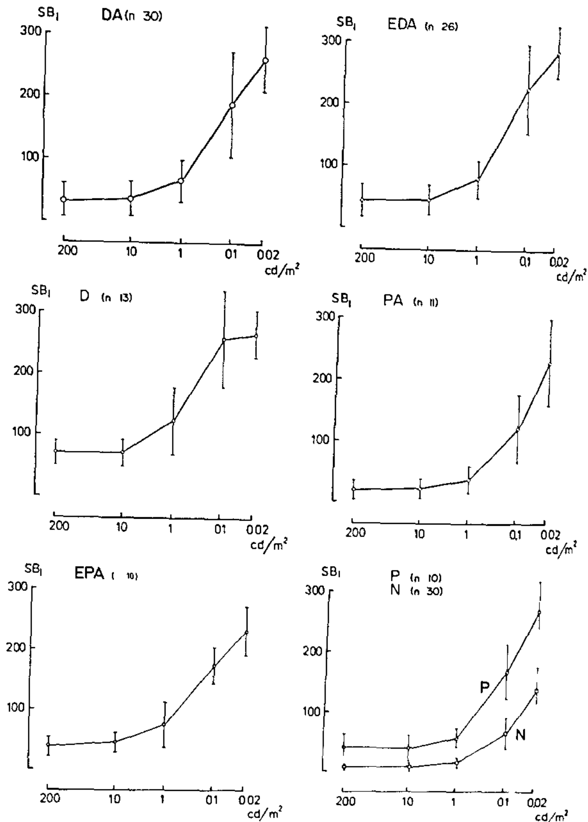
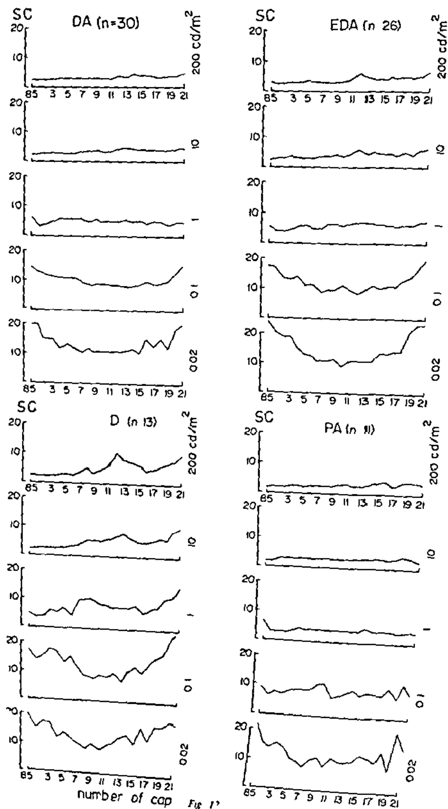
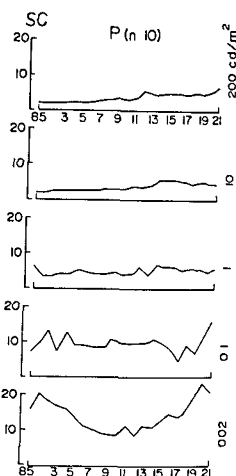


Fig 11

Mean error scores (SB_I) obtained with the first box of colour caps numbered 85 (red) to 21 (greenish yellow) of the Farnsworth Munsell 100 hue test (F100) at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² Results obtained in subjects with defective colour vision (classified with the Nagel anomaloscope) as well as in a series of normal subjects are shown Vertical bars indicate 2 × standard deviation


SC
DA (n=30)
EDA (n 26)
D (n 13)
PA (n 11)
200 cd/m2
10
1
01
002
85 3 5 7 9 11 13 15 17 19 21
number of cap
Fig 1?



Figs 12 and 13

Diagrams showing the distribution of the mean error score of each separate colour cap (SC) of the first box caps numbered 85 (red) to 21 (greenish yellow) of the Farnsworth Munsell 100 hue test (F100) obtained at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² Results obtained in subjects with defective colour vision (classified with the Nagel anomaloscope) as well as in a series of normal subjects are shown

Fig 13

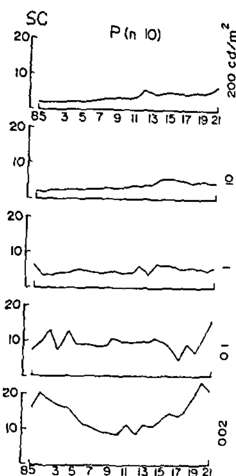
with the SB, obtained at 200 cd/m² is statistically significantly higher ($P < 0.05$) in the series of normal subjects as well as in all subjects with red green defects excluding the groups of the protanopes (P value of the protanopes 0 113)

Figs 12 and 13 illustrate the distribution of the mean error score of each separate colour cap (SC) obtained with caps numbered 85 to 21 (first box) of the F100 test performed at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² At low luminance levels (0 1 and 0 02 cd/m²) in those subjects with defective colour vision a relatively larger mean error score is obtained with caps with red (to the left) or greenish yellow (to the right) hues compared with the score obtained with yellowish red and yellow hues (in the center) In normal subjects there is at 0 1 and 0 02 cd/m² a slight relative increase in the mean error score from the right end of the scale (cap number 21 yellowish green) towards the left end (cap number 85 red)

Figs 14 and 15 illustrate the results obtained in the Panel D 15 dichotomous test (F15) by 100 subjects with red green defects of colour vision at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² (see methods and Table 1) It is evident from these illustrations that at 200 and 10 cd/m² luminosity levels a large number of protan (Pr) and deutan (De) types of confusion axes are found in subjects with all types of red green defects the number of tritan (Tr) tetartan (Te) and scotopic (S) types of confusion increasing first at the lowest luminosity levels (0 1 and 0 02 cd/m²) At luminosity levels of 200 10 and 1 cd/m² all normal subjects passes the F15 test without errors Blue yellow types of confusion (Fig 16) appeared at 0 1 cd/m² and their number increased at 0 02 cd/m² There are no scotopic type of confusion in the normal subjects at 0 1 cd/m² while in subjects with red green defects (Figs 14 and 15 particularly in subjects with deutan types of the defect) scotopic confusions dominate at this luminosity level At 0 02 cd/m² scotopic confusions dominate in subjects with both protan and deutan types of the defect excluding those with protanomaly and extreme protanomaly A statistical analysis of the results showed that in all groups of subjects with red green defects there was a larger number of scotopic type of confusions at 0 02 cd/m² compared with the series of normal subjects ($P < 0.01$) Typical results of the F15 test obtained by individual subjects of different types of red green defects are illustrated in Fig 17

The mean number of misread plates in the Bostrom Kugelberg pseudo isochromatic test (BK II) obtained at five background luminosity levels 200 10 1 0 1 and 0 02 cd/m² are illustrated in Fig 18 Results obtained by 100 subjects with different types and degrees of red green defects and by 30 normal subjects are shown The vertical bars illustrate twice the standard deviation At 200 cd/m²

SC
EPA (n 10)
200 cd/m²
10
1
01
002
85 3 5 7 9 11 13 15 17 19 21



SC
N (n 30)
200 cd/m²
10
1
01
002
85 3 5 7 9 11 13 15 17 19 21
number of cap

Figs 1? and 13

Diagrams showing the distribution of the mean error score of each separate colour cap (SC) of the first box caps numbered 85 (red) to 21 (greenish yellow) of the Farnsworth Munsell 100 hue test (F100) obtained at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² Results obtained in subjects with defective colour vision (classified with the Nagel anomaloscope) as well as in a series of normal subjects are shown

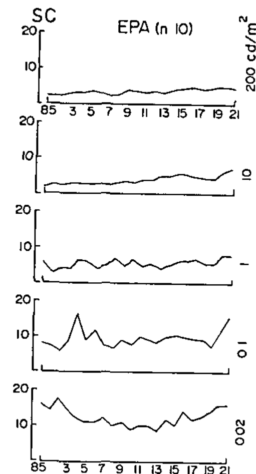
Fig 13

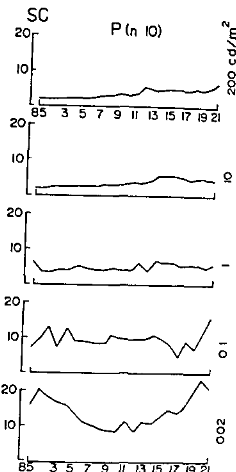
with the SB_1 obtained at 200 cd/m² is statistically significantly higher ($P < 0.05$) in the series of normal subjects as well as in all subjects with red green defects excluding the groups of the protanopes (P value of the protanopes 0 113)

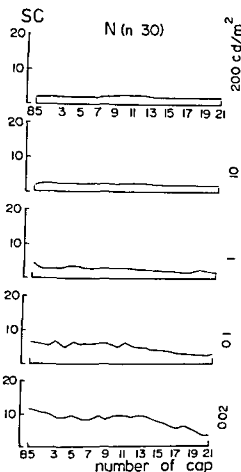
Figs 12 and 13 illustrate the distribution of the mean error score of each separate colour cap (SC) obtained with caps numbered 85 to 21 (first box) of the F100 test performed at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² At low luminance levels (0 1 and 0 02 cd/m²) in those subjects with defective colour vision a relatively larger mean error score is obtained with caps with red (to the left) or greenish yellow (to the right) hues compared with the score obtained with yellowish red and yellow hues (in the center) In normal subjects there is at 0 1 and 0 02 cd/m² a slight relative increase in the mean error score from the right end of the scale (cap number 21 yellowish green) towards the left end (cap number 85 red)

Figs 14 and 15 illustrate the results obtained in the Panel D 15 dichotomous test (F15) by 100 subjects with red green defects of colour vision at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² (see methods and Table 1) It is evident from these illustrations that at 200 and 10 cd/m² luminosity levels a large number of protan (Pr) and deutan (De) types of confusion axes are found in subjects with all types of red green defects the number of tritan (Tr) tetartan (Te) and scotopic (S) types of confusion increasing first at the lowest luminosity levels (0 1 and 0 02 cd/m²) At luminosity levels of 200 10 and 1 cd/m² all normal subjects passes the F15 test without errors Blue yellow types of confusion (Fig 16) appeared at 0 1 cd/m² and their number increased at 0 02 cd/m² There are no scotopic type of confusion in the normal subjects at 0 1 cd/m² while in subjects with red green defects (Figs 14 and 15 particularly in subjects with deutan types of the defect) scotopic confusions dominate at this luminosity level At 0 02 cd/m² scotopic confusions dominate in subjects with both protan and deutan types of the defect excluding those with protanomaly and extreme protanomaly A statistical analysis of the results showed that in all groups of subjects with red green defects there was a larger number of scotopic type of confusions at 0 02 cd/m² compared with the series of normal subjects ($P < 0.01$) Typical results of the F15 test obtained by individual subjects of different types of red green defects are illustrated in Fig 17

The mean number of misread plates in the Bostrom Kugelberg pseudo isochromatic test (BK II) obtained at five background luminosity levels 200 10 1 0 1 and 0 02 cd/m² are illustrated in Fig 18 Results obtained by 100 subjects with different types and degrees of red green defects and by 30 normal subjects are shown The vertical bars illustrate twice the standard deviation At 200 cd/m²







Figs 12 and 13

Diagrams showing the distribution of the mean error score of each separate colour cap (SC) of the first box caps numbered 85 (red) to 21 (greenish yellow) of the Farnsworth Munsell 100 hue test (F100) obtained at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² Results obtained in subjects with defective colour vision (classified with the Nagel anomaloscope) as well as in a series of normal subjects are shown

Fig 13

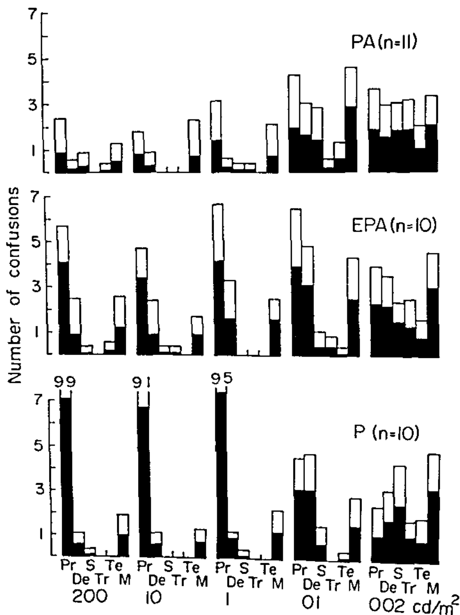


Fig 15

or minor errors (M), obtained with the Panel D 15 dichotomous test (F15) at background lum nosity le els of 200 10 1 0 1 and 0 02 cd/m² Results obtained by subjects with defective colour vision (classifed with the Nagel anomaloscope) are shown

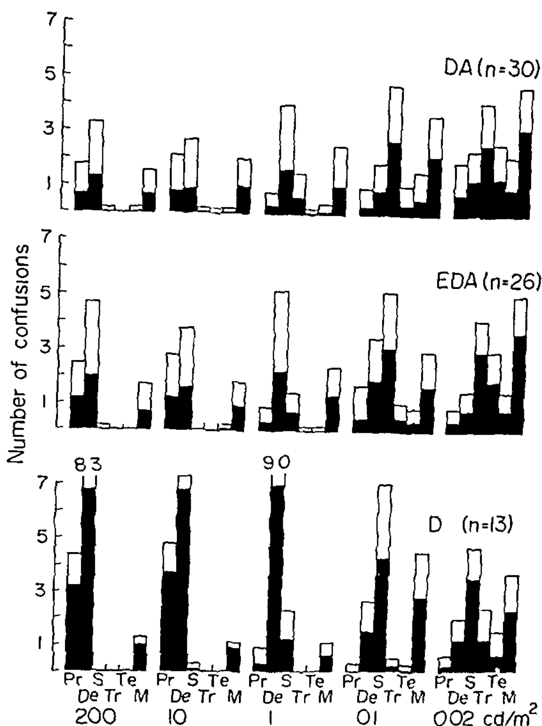


Fig 14

Figs 14 and 15

Histograms showing the mean number (black oblongs the white oblongs show the standard deviation) of protan (Pr) deutan (De) scotopic (S) tritan (Tr) and tetartan (Te) types of confusion

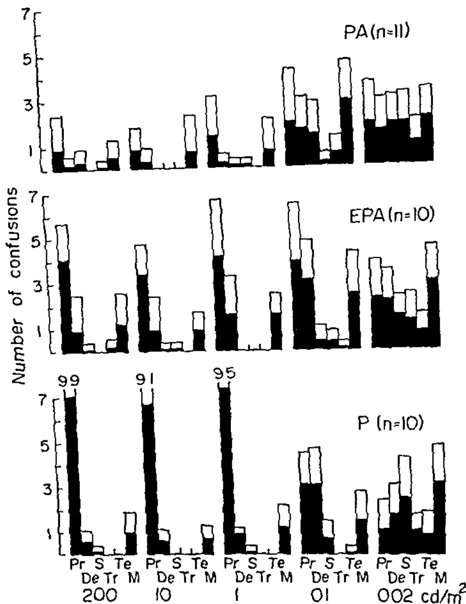


Fig 15

or minor errors (M), obtained with *the Panel D-15* dichotomous test (F15) at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m^2 Results obtained by *subjects* with *defective* colour vision (class fied with the Nagel *anomaloscope) are shown*

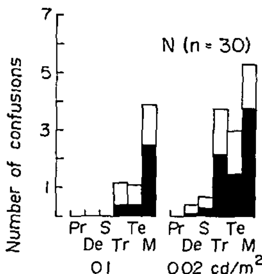


Fig 16
Histograms showing the mean number (black oblongs the white oblongs show the standard deviation) of protan (Pr), deutan (De) scotopic (S) tritan (Tr) and tetartan (Te) types of confusion or minor errors (M) obtained with the Panel D 15 dichotomous test (F15) by 30 normal subjects at background luminosity levels of 0 1 and 0 02 cd/m²

subjects with deuteranomaly made on average 9 2 misreadings compared with 7 7 in subjects with protanomaly (note the large stadard deviation in the results of subjects with protanomaly at 200, 10 and 1 cd/m²) At 0 02 cd/m² subjects *with deuteranomaly made on average 13 6 misreadings compared with 14 1 in* subjects with protanomaly Subjects with extreme deuteranomaly made on average 11 2 misreadings at 200 cd/m² and 13 3 misreadings at 0 02 cd/m², the corresponding values in subjects with extreme protanomaly being 11 6 and 14 5 Subjects with deuteranopia made on average 12 2 misreadings at 200 cd/m² and 14 2 misreadings at 0 02 cd/m², the corresponding values in subjects with

Fig 17
Typical results obtained with the Panel D 15 dichotomous test (F15) by individual subjects (classified with the Nagel anomaloscope) with deuteranomaly (DA) extreme deuteranomaly (EDA) *deuteranopia (D) protanomaly (PA) extreme protanomaly* (EPA) protanopia (P) and a normal subject (N) The subjects were tested at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m²

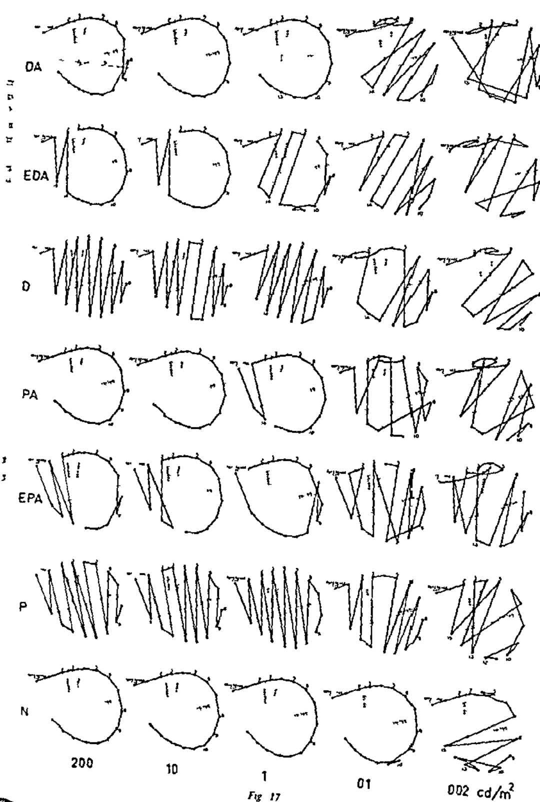


Fig 17

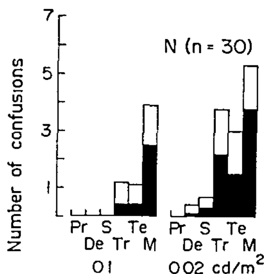


Fig 16
Histograms showing the mean number (black oblongs the white oblongs show the standard deviation) of protan (Pr), deutan (De) scotopic (S) tritan (Tr) and tetartan (Te) types of confusion or minor errors (M) obtained with the Panel D 15 dichotomous test (F15) by 30 normal subjects at background luminosity levels of 0 1 and 0 02 cd/m²

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Fig 17
Typical results obtained with the Panel D 15 dichotomous test (F15) by individual subjects (classified with the Nagel anomaloscope) with deuteranomaly (DA) extreme deuteranomaly (EDA) deuteranopia (D) protanomaly (PA) extreme protanomaly (EPA) protanopia (P) and a normal subject (N) The subjects were tested at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m²

protanopia being 11 9 and 14 1 (note the small standard deviation in the results of subjects with deuteranopia at all five luminance levels) This illustration also shows that normal subjects made no misreadings in the BK II test at 200 and 10 cd/m² luminosity levels and they made on average 0 2 5 6 and 10 4 misreadings at respective luminosity levels of 1, 0 1 and 0 02 cd/m²

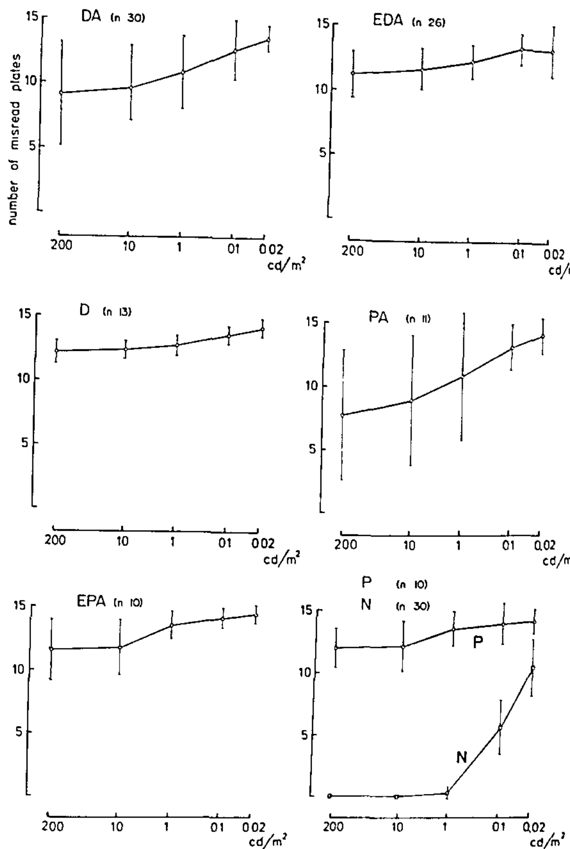


Fig 18

Diagrams showing the mean number of misread plates (vertical bars show 2 × standard deviation) in the Bostrom Kugelberg (BK II) pseudo isochromatic test obtained at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² Results obtained by subjects with defective colour vision (classified with the Nagel anomalscope) as well as by a series of normal subjects are shown

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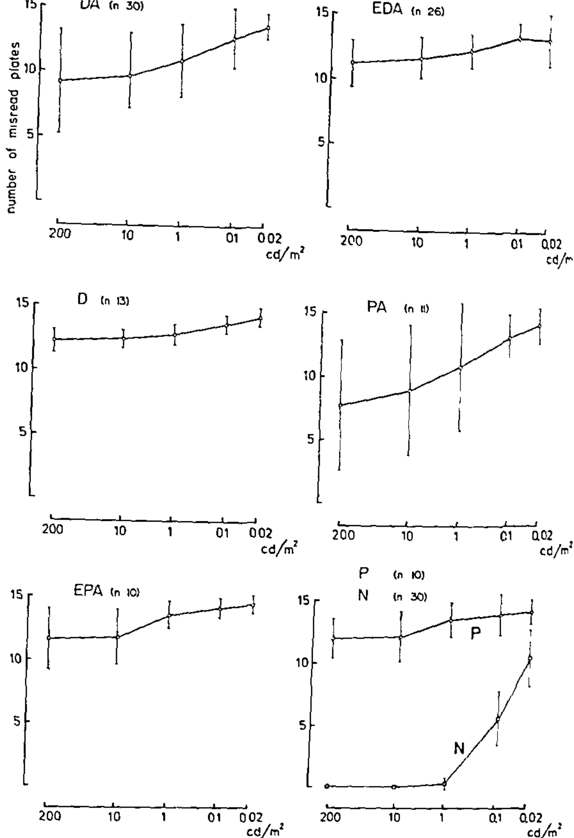


Fig 18

Diagrams showing the mean number of misread plates (vertical bars show 2 × standard deviation) in the Boström Kugelberg (BK II) pseudo-isochromatic test, obtained at background luminosity levels of 200 10 1 0 1 and 0 02 cd/m² Results obtained by subjects with defective colour vision (classified with the Nagel anomalscope) as well as by a series of normal subjects are shown

protanopia being 11 9 and 14 1 (note the small standard deviation in the results of subjects with deuteranopia at all five luminance levels) This illustration also shows that normal subjects made no misreadings in the BK II test at 200 and 10 cd/m² luminosity levels and they made on average 0 2, 5 6 and 10 4 misreadings at respective luminosity levels of 1 0 1 and 0 02 cd/m²

DISCUSSION

The results of the present study show that the colour discrimination of subjects with congenital red green defects as measured with the Farnsworth Munsell 100 hue test, is much lower in mesopic (0.1 cd/m^2) conditions compared with results obtained in photopic (200 cd/m^2) ones. An increase in the error scores caused by reduced illumination indicating a reduction of both red green and blue yellow discrimination is evident in all groups of subjects with red green defects. Interestingly in low illumination the error score indicating a tritan type of the defect increased markedly in subjects with all types of red green defects and clearly exceeds the error score indicating a physiological tritan type of the defect typical of normal subjects examined at mesopic (0.1 cd/m^2) luminance level.

The maximal luminance level of 200 cd/m^2 used in the present study refers to the neutral grey background of the Macbeth illuminator and not to the luminance of the surface of the colour caps. At 200 cd/m^2 background illumination the luminance of the colour caps was measured as 120 cd/m^2 and was independent of the colour of the cap (see methods). The neutral density filters used in the present study do not show a marked deviation from neutrality within the range of the dominant wavelengths (445 to 633 nm) of the F100 test (Figs. 1 and 3). Thus the two lowest background luminance levels 0.1 and 0.02 cd/m^2 are almost identical with the illumination levels of 1 and 0.216 lux (0.06 and 0.014 cd/m^2 luminance of the colour caps) used in the investigations of Verriest et al. (1963) showing a tritan type of distribution of the normal mean error score (25 normal subjects) at 1 lux illumination. In their results the error maxima pointed to colour caps numbered 4 and 49 at 1 lux illumination and to caps numbered 6 and 50 at 0.216 lux. Apparently at 0.1 cd/m^2 backgrounds used as the standard mesopic luminance level in the present study the photopic distribution of the normal spectral luminosity function dominates, i.e. the rod function and consequent scotopic luminosity distribution do not effectively contribute to the results. In the results of Verriest et al. (1963) the scotopic luminosity function dominates at illumination levels of 0.100 and 0.046 lux resulting in normal subjects in an arrangement of the colour caps fully independent of the colour. In their results the maxima of the normal mean error score obtained at 0.046 lux illumination point to the caps numbered 12 and 54

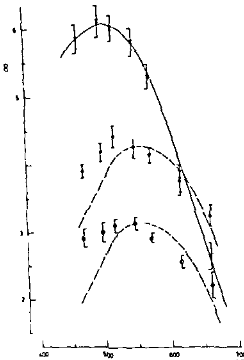


Fig 19
Averaged spectral sensitivity curves of normal healthy eyes (unpublished results of Elenius and Airas) obtained in the dark adapted eye tested 15 peripherally (crosses) as well as by using backgrounds of 0 25 cd/m² (dots) and 10 cd/m² (circles) and tested with the central fixation of the test object. The vertical bars show twice the standard deviation The measurements were made with a Goldmann perimeter provided with calibrated interference and neutral filters test area 64 mm² 500 msec flashes at 15 sec intervals The solid line and the interrupted line refer to the CIE standard scotopic and photopic luminosity curves respectively The crosses refer to the averages of 5 subjects and the dots and circles those of 10 subjects

Unpublished results of Elenius and Airas (1980) illustrated in Fig 19 show the average spectral sensitivity curves of normal subjects obtained in the dark adapted eye (tested 15 peripherally) as well as the results obtained by using backgrounds of 0 25 and 10 cd/m² luminance (tested with the central fixation of the test object) The measurements were made by using a Goldmann static perimeter provided with calibrated interference and neutral filters (test area 64 mm² 500 msec flashes at 15 sec intervals) The curves obtained with 0 25 and 10 cd/m² background are broader than the CIE photopic luminosity curve Compared with the curve obtained with 0 25 cd/m² background that obtained after one hour of dark adaptation (no background illumination) shows only a slight alteration in sensitivity for the red test lights but a large increase in

sensitivity for green and blue lights The results are in agreement with those of Kinney (1955) indicating a contribution of both rod and cone mechanisms to the intermediate sensitivity curves obtained in mesopic conditions Interestingly however, even at 10 cd/m² background (normally used in the Goldmann perimeter) a broad (intermediary) type of the spectral sensitivity curve is obtained

Results obtained (at the threshold of vision) with spectral lights projected on a ' white" background cannot be quantitatively related to those obtained with tests based on pigment colours (colour caps with a black surrounding rim) presented on a grey background Therefore the curves of Fig 19 only provide an approximate idea of a part of the Purkinje shift (from an intermediate type of spectral sensitivity to full dominance of the rod mechanism) occuring below a background luminance level of 0 25 cd/m² Moreover the spectral sensitivity curves obtained with spectral lights show a great variation depending on the experimental conditions The relative contributions of the ' luminance system and the ' opponent colour system" to the photopic spectral sensitivity curves of normal human observers, and the variation of the results depending on the test area and duration, as well as the type of background, have been recently discussed by King Smith and Carden (1976) and by Ingling (1978) These authors also present interpretations of the psychophysical results in electrophysiological terms of the "tonic and "phasic' behavior of the retinal ganglion cells of the rhesus monkey (Gouras 1968, De Monasterio and Gouras 1975)

It is particularly interesting to compare the results of colour defective subjects in the present study measured in quadrants II and IV of the F100 test (error score $S_2 + S_4$) obtained at 200 and 0 1 cd/m² background It should be noted that all types of colour defective subjects made relatively few errors in quadrants II and IV when examined at photopic illumination For example the mean error score $S_2 + S_4$ of subjects with deuteranopia (Table 3) is 21 8 ± 11 4 at 200 cd/m² compared with 17 4 ± 15 8 in the series of normal subjects At 0 1 cd/m² the mean error score $S_2 + S_4$ of subjects with deuteranopia increased to 293 8 ± 77 9 compared with 130 0 ± 44 5 in normal subjects In subjects with deuteranopia the maxima of the increase in errors in quadrant IV are located at caps 4 and 0 (Fig 6, D 0 1 and Dd) indicating a tritan type of the defect (decrease in blue yellow discrimination)

The results illustrated in Fig 6 (D0 1 cd/m²) are reminiscent of those obtained in subjects with autosomal recessive incomplete achromatopsia with a deutan type of photopic luminosity function described by *Smith et al (1979) These* subjects show preserved photopic electro retinograms a high flicker fusion

frequency scotopic results in the Panel D 15 test, and are assumed to have (in colour matching tests) trichromatic colour vision based on functioning short and long wavelength absorbing cones and a rhodopsin containing receptor

Another type of autosomal recessive incomplete achromatopsia with a protan type of luminosity function (Smith et al 1978) shows the results obtained with the F100 test reminiscent of those obtained in the present study in subjects with protanopia examined in mesopic conditions (Fig 7 P0 1) One of the subjects examined by Smith et al (1978) was shown to have dichromatic colour vision based on normal rhodopsin rods and a cone receptor absorbing maximally at 545 nm. There was a minimal photopic electroretinogram activity present in this subject.

The increase in the number of errors made by the red green defective subjects in quadrant IV of the F100 test in reduced illumination is evident also in the illustrations of Figs 12 and 13 showing the results obtained with separate colour caps numbered 85 to 21 (first box) There is a relative increase from cap 7 (limit of quadrant IV) towards red hues (to left) At 0 1 cd/m² this tendency is more marked in subjects with deutan types of the defect compared with those with protan defects while at 0 02 cd/m² this tendency is evident in subjects with all types of red green defects as well as in normal subjects The increase in the number of errors from center towards the cap number 21 (to right) indicates a further decrease in red green discrimination in subjects with red green defects examined in low illumination This tendency is absent in normal subjects Interestingly in the colour defective subjects there is no relative increase in the number of errors at 0 1 or 0 02 cd/m² luminance level at a location indicating an arrangement of the caps independent of their colour i e an arrangement based only on the scotopic luminosity values of the caps (maximum at cap 12 Verriest et al 1963) However disregarding the four peaks (as well as the division of the errors in four quadrants) of the result of the F100 test obtained at 0 1 cd/m² in subjects with deuteranopia the maxima of the mean total error score would indicate scotopization of the visual function

Sloan (1954) showed that most subjects with congenital total colour blindness arranged the colour caps of the Panel D 15 dichotomous test in order *of their decreasing* scotopic reflectance In her measurements the blue pilot cap of this test (Munsell colour 10 B) showed the highest scotopic relative *reflectance* (0 3190) while cap number 9 (Munsell colour 10 YR) showed the lowest one (0 1306) Normal subjects of the present study passed the F15 test without errors at backgrounds 200 10 and 1 cd/m² Blue *yellow (tritan)* confusions appeared at 0 1 cd/m² and their average number increased at 0 02 cd/m², while there were no scotopic confusions in the normal subjects at 0 1 cd/m² and a very low average

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number of scotopic confusions at 0 02 cd/m² background These results are in agreement with those of Verriest et al (1963) who found a tritan type of confusion axis at 1 lux illumination in 12 per cent of their normal subjects and in 32 per cent at 0 216 lux respectively They found a scotopic type of confusion axis in 24 per cent of the normal subjects at 0 216 lux, in 60 per cent at 0 1 lux and in 80 per cent at 0 046 lux illumination In contrast to the results obtained in normal subjects, the scotopic type of confusions dominates in subjects with a deutan type of defect of the present study already at 0 1 cd/m² The average number of tritan type of confusions increased in these subjects first at 0 02 cd/m background In subjects with a protan type of the defect, the average number of both scotopic and tritan type of confusions increased markedly first at 0 02 cd/m² background In these subjects the average number of scotopic confusions is low at 0 1 cd/m² background excluding subjects with protanomaly In all subjects with red green defects, excluding those with protanomaly and extreme protanomaly, the scotopic type of confusions dominates at 0 02 cd/m²

The series of measurements performed in the present study at decreased background levels were made binocularly by using equal pairs of neutral density filters The glasses with neutral filters were changed in a dim red light (Macbeth illuminator extinguished) and at background luminance levels of 0 1 and 0 02 cd/m² the subjects were allowed to dark adapt for 3 minutes before the measurements were continued (see methods) This procedure was considered to provide a sufficiently complete adaptation to the respective backgrounds

The following confirmatory experiment was performed in the course of the present study on 5 normal subjects and on 10 subjects with the following types and numbers of cases with red green defects, DA 1 EDA 5 D 1 EPA 2 and P, 1 The subject to be examined was first light adapted for 15 minutes to the 200 cd/m² background of the Macbeth illuminator and then the time required for dark adaptation to backgrounds of 0 1 and 0 02 cd/m² was measured in two separate experiments The test object was a 3 × 3 cm square grey paper (Munsell neutral grey N 6 with an equal reflectance 30 per cent compared with the background of the illuminator) provided with a central 11 × 11 mm (2°) square of the next grey paper with a higher reflectance in the Munsell series of 36 matte neutral greys (N 6 25 reflectance 33 per cent) The subjects with red green defects were able to perceive the central increment of light of the test object after 1 to 20 sec (normals saw it without delay) at 0 1 cd/m² and after 15 to 45 sec (normals after 1 to 45 sec) at 0 02 cd/m² background It should be noted that the luminance of the central test spot is about 10 per cent higher than the background, while the luminance of the colour caps (surrounded by a black rim) is about 40 per cent below the grey background During these experiments it was

also observed that normal subjects identified the colour of a red, green and blue colour cap (number 1 36 and 54 of the F100 test) used as controls within the short periods of dark adaptation mentioned above

By juxtaposition of the curves of dark adaptation (no background) and the increment thresholds obtained at different backgrounds Crawford (1947) showed that the thresholds obtained at any time in the dark can be reproduced for each different size of the test field by an appropriate background luminance Crawford s data were obtained after a relatively weak light adaptation (dark adaptation completed in 15 minutes) However the measurements made on a rod monochromat (Blakemore and Rushton 1965) and in the normal human fovea (DuCroz and Rushton 1966) have confirmed the "equivalent background principle" over a large range of visual thresholds

It has been assumed that an alteration at the level of receptors is the main cause of the congenital red green defects of colour vision This "alteration" has been located in the visual pigments of the different types of cones of the human retina (Rushton et al 1973 Piantanida and Sperling 1973 a and b) Their results show that the absorption curve of the most red sensitive pigment of protanomalous subjects is dislocated towards shorter wavelengths (maximum at 545 to 550 nm compared with 570 nm in normal subjects) In subjects with deuteranomaly the maximum of the maximally green sensitive pigment is dislocated from the normal 535 nm to 555 to 560 nm This indicates that in subjects with anomalous trichromatism the cause of the defective colour vision is the location of the absorption maxima of the long and medium wavelength absorbing cones quite close to each other In subjects with a red green dichromacy the long or medium wavelength absorbing cone pigment has been shown to be totally missing (Rushton 1963 a b and c 1965 a and b) Thus the protanopes have a normal 535 nm pigment but no 570 nm one while in the deuteranopes there is a normal 570 nm pigment and the 535 nm one is missing It is further assumed that in both types of the red green dichromats there is a normal blue sensitive pigment absorbing maximally at 445 nm This pigment however cannot be measured by the use of the method of reflexion densitometry

Returning to the interpretation of the results of the present study there is no reason to assume that an inherited defect in the function of the blue cones themselves in subjects with congenital defects of red green colour vision could be the cause of the remarkable sensitivity (earlier reduction compared with normals) of the remaining blue yellow discrimination to the reduction of the background luminance level observed in these subjects It is more tempting to assume that the retinal organization of the "blue yellow opponent colour mechanism" is brought out of normal function due to a defective antagonism

number of scotopic confusions at 0 02 cd/m^2 background These results are in agreement with those of Verriest et al (1963), who found a tritan type of confusion axis at 1 lux illumination in 12 per cent of their normal subjects and in 32 per cent at 0 216 lux respectively They found a scotopic type of confusion axis in 24 per cent of the normal subjects at 0 216 lux in 60 per cent at 0 1 lux and in 80 per cent at 0 046 lux illumination In contrast to the results obtained in normal subjects, the scotopic type of confusions dominates in subjects with a deutan type of defect of the present study already at 0 1 cd/m^2 The average number of tritan type of confusions increased in these subjects first at 0 02 cd/m^2 background In subjects with a protan type of the defect, the average number of both scotopic and tritan type of confusions increased markedly first at 0 02 cd/m^2 background In these subjects the average number of scotopic confusions is low at 0 1 cd/m^2 background excluding subjects with protanomaly In all subjects with red green defects, excluding those with protanomaly and extreme protanomaly, the scotopic type of confusions dominates at 0 02 cd/m^2

The series of measurements performed in the present study at decreased background levels were made binocularly by using equal pairs of neutral density filters The glasses with neutral filters were changed in a dim red light (Macbeth illuminator extinguished) and at background luminance levels of 0 1 and 0 02 cd/m^2 the subjects were allowed to dark adapt for 3 minutes before the measurements were continued (see methods) This procedure was considered to provide a sufficiently complete adaptation to the respective backgrounds

The following confirmatory experiment was performed in the course of the present study on 5 normal subjects and on 10 subjects with the following types and numbers of cases with red green defects DA 1 EDA, 5, D 1 EPA 2 and P, 1 The subject to be examined was first light adapted for 15 minutes to the 200 cd/m^2 background of the Macbeth illuminator and then the time required for dark adaptation to backgrounds of 0 1 and 0 02 cd/m^2 was measured in two separate experiments The test object was a 3 × 3 cm square grey paper (Munsell neutral grey N 6, with an equal reflectance 30 per cent compared with the background of the illuminator) provided with a central 11 × 11 mm (2°) square of the next grey paper with a higher reflectance in the Munsell series of 36 matte neutral greys (N 6 25, reflectance 33 per cent) The subjects with red green defects were able to perceive the central increment of light of the test object after 1 to 20 sec (normals saw it without delay) at 0 1 cd/m^2 and after 15 to 45 sec (normals after 1 to 45 sec) at 0 02 cd/m^2 background It should be noted that the luminance of the central test spot is about 10 per cent higher than the background, while the luminance of the colour caps (surrounded by a black rim) is about 40 per cent below the grey background During these experiments it was

SUMMARY AND CONCLUSIONS

The effects of reduced illumination on the results obtained with the Farnsworth Munsell 100 hue test (F100) the Panel D 15 dichotomous test (F15) and the Bostrom Kugelberg pseudo isochromatic test (BK II 1972) were investigated

The material comprised 100 red green defective subjects (30 cases with deuteranomaly 26 with extreme deuteranomaly 13 with deuteranopia 11 with protanomaly 10 with extreme protanomaly and 10 with protanopia) as well as 30 normal subjects all classified with the Nagel anomaloscope

A Macbeth daylight illuminator was used and its maximal background (200 cd/m^2) was reduced by using pairs of calibrated neutral filters mounted on four pairs of welder s glasses Measurements were made at five different backgrounds 200 10 1 0 1 and 0 02 cd/m^2

The results of the F100 test were analysed on the basis of a division of the Farnsworth colour circle in four equal quadrants showing in the results obtained with subjects with red green dichromacy a high totalled error score in the opposite quadrants I and III ($S_1 + S_3$) and a low totalled error score in the opposite quadrants II and IV ($S_2 + S_4$)

The results of the F15 test were analysed by using a modification of the test chart of Verriest et al (1963)

With a reduction of the background luminance level from 200 to 0 1 cd/m^2 there was a larger increase in both the total error score (ST) and in scores S_1 + S_3 and $S_2 + S_4$ obtained with subjects with all types of red green defects than with normal subjects (P value of the Student s t test < 0 05) At 0 1 cd/m^2 the results of the red green defective subjects (based on the distribution of the total error score of the F100 test) indicated a scotopization" of the visual function however the separate scores $S_1 + S_3$ and $S_2 + S_4$ indicated a decrease in red green and blue yellow discrimination The increase in the tritan type of the defect ($S_2 + S_4$) found in the red green defective subjects at 0 1 cd/m^2 background was significantly larger than the "physiological tritanopia" observed in normal subjects in the same condition

In all types of red green defective subjects a reduction of the background luminance from 200 to 0 1 cd/m^2 caused an equal increase in the total error

exerted by the long and medium wavelength absorbing cones (of the red green *defective subjects) in low background illumination* Likewise the "scotopization at low illumination observed in the red green defective subjects at a higher background luminance compared with normals, is likely to be caused by a weaker than normal ' dominance' of the cone mechanism', over a normal ' rod mechanism" in these subjects

As already mentioned in the introduction, very few earlier observations indicate a defective function of the "blue yellow mechanism of the red green defective subjects at low illumination In perimetric retinal profiles Verriest and Uvijls (1977) have described a deeper than normal scotoma for short *wavelengths of light in protan and deutan (and also in tritan) types of the defect* examined at 3 16 cd/m^2 background luminance Accordingly, it was observed by Walraven and Leebeek (1960) that at 0 1 lux illumination colour defective subjects classified as 'mild' in the H R R test made, compared with normals, proportionally more blue yellow than red green mistakes

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score (ST) Only in subjects with extreme deuteranomaly was the increase in the ST suggestively larger (P = 0 086) compared with subjects with protanopia

The results obtained in the F100 test by subjects with deuteranopia at 0 1 cd/m² background appeared to be similar to the results obtained by Smith et al (1979) in subjects with 'autosomal recessive incomplete achromatopsia with a deutan type of luminosity function" Likewise the results obtained in the present study in subjects with protanopia (at 0 1 cd/m²) are reminiscent of those obtained in autosomal recessive incomplete achromatopsia with a protan type of luminosity function' (Smith et al 1978)

In the results of the F15 test, a scotopic axis was found at a higher background luminance level in the red green defective subjects compared with normals In subjects with a deutan type of the defect, a scotopic type of confusion dominated at 0 1 cd/m², and in all types of red green defective subjects excluding those with protanomaly and extreme protanomaly, a scotopic confusion dominated at 0 02 cd/m² In normal subjects no scotopic confusions were observed at 0 1 cd/m² and a tritan type of confusion dominated at 0 02 *cd/m² background At 0 02 cd/m² scotopic confusions were found significantly* more often (P < 0 01) in the red green defective subjects compared with normals

The pseudo isochromatic plates of Bostrom Kugelberg (BK II, 1972) are designed to detect red green defects of colour vision (there are no plates included in this series for detection of blue yellow defects) The relatively high number of misreadings made by most subjects with red green defects at 200 cd/m² limited *the increase in the number of misreadings made at low illumination* The number of misreadings made by normal subjects in the BK II test shows a marked increase at background luminance levels below 0 1 cd/m²

It is tentatively concluded on the basis of the results of the present study that the more marked reduction caused by low background luminance, of the remaining blue yellow discrimination observed in the congenitally red green defective subjects compared with normals may be caused by an abnormal function of the blue yellow opponent colour mechanism due to a defective antagonism exerted by the medium and/or long wavelength absorbing cones (on the short wavelength absorbing cones) in the red green defective subjects examined in reduced illumination

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score (ST). Only in subjects with extreme deuteranomaly was the increase in the ST suggestively larger (P = 0.086) compared with subjects with protanopia.

The results obtained in the F100 test by subjects with deuteranopia at 0.1 cd/m² background appeared to be similar to the results obtained by Smith et al. (1979) in subjects with "autosomal recessive incomplete achromatopsia with a deutan type of luminosity function". Likewise the results obtained in the present study in subjects with protanopia (at 0.1 cd/m²) are reminiscent of those obtained in "autosomal recessive incomplete achromatopsia with a protan type of luminosity function" (Smith et al. 1978).

In the results of the F15 test, a scotopic axis was found at a higher background luminance level in the red-green defective subjects compared with normals. In subjects with a deutan type of the defect a scotopic type of confusion dominated at 0.1 cd/m² and in all types of red-green defective subjects excluding those with protanomaly and extreme protanomaly, a scotopic confusion dominated at 0.02 cd/m². In normal subjects no scotopic confusions were observed at 0.1 cd/m² and a tritan type of confusion dominated at 0.02 cd/m² background. At 0.02 cd/m² scotopic confusions were found significantly more often (P < 0.01) in the red-green defective subjects compared with normals.

The pseudo-isochromatic plates of Bostrom-Kugelberg (BK II, 1972) are designed to detect red-green defects of colour vision (there are no plates included in this series for detection of blue-yellow defects). The relatively high number of misreadings made by most subjects with red-green defects at 200 cd/m² limited the increase in the number of misreadings made at low illumination. The number of misreadings made by normal subjects in the BK II test, shows a marked increase at background luminance levels below 0.1 cd/m².

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by

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Sarcoidosis is a »multisystem granulomatous disorder of unknown etiology most commonly affecting young adults and presenting most frequently with bilateral hilar lymphadenopathy pulmonary infiltration skin or eye lesions » (James et al 1976c)

The uveoparotid fever described by Heerfordt in 1909 was later found to be a manifestation of sarcoidosis (Bruins Slot 1936) and since then numerous reports on the various ophthalmic changes in sarcoidosis have been published (Longcope & Freiman 1952 Crick et al 1961 James et al 1964)

The frequency of ocular manifestations varies a great deal depending on how the materials have been selected and how thoroughly the eyes have been examined (Longcope & Freiman 1952 James et al 1964) The varying part played by sarcoidosis in the etiology of uveitis — the complications of which may lead to deterioration of the vision or even to blindness — has begun to attract increasing interest (Perkins 1968 Uyama 1972 James et al 1976a) Other manifestations of sarcoidosis in the eye and its adnexa have received less attention These include sarcoidosis of the lacrimal apparatus band keratopathy and conjunctival changes Conjunctival granulomatosis however might well be assumed to be the most common of the ophthalmic manifestations of sarcoidosis since the conjunctiva contains lymphatic tissue readily affected by this disorder

In Scandinavia where research into sarcoidosis has otherwise been lively (e g Boeck 1899 Schaumann 1936 Putkonen 1943 Löfgren 1953a 1953b) the eyes of patients with sarcoidosis have not been thoroughly examined For this reason it appeared of interest to investigate the situation regarding ocular sarcoidosis in Finland Mass chest radiography in this country has revealed numerous symptom free patients with pulmonary sarcoidosis and the prognosis of the disease has been considered favourable (Selroos 1969)

The ophthalmologist is in a unique position when examining patients with sarcoidosis, for the eye is the only part of the body where granulomas can readily be recognised and their clinical behaviour observed

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The purpose of the present work was to study

- the frequency and type of the ophthalmic changes in patients with sarcoidosis
- other changes attributable to sarcoidosis seen in patients in whom the eye or its adnexa are affected
- the characteristics and course of sarcoid uveitis as well as its prognosis
- the diagnostic role of conjunctival biopsy and its assessment

II REVIEW OF THE LITERATURE

A Ophthalmic manifestations

1 FREQUENCY

The first attempt to throw light on ocular sarcoidosis was made in 1939 by Österberg He collected 27 cases of iritis from among 500 patients with sarcoidosis mostly reported in dermatological literature and concluded that iritis Boeck is a rare disease Two years after Österberg however among 100 patients with sarcoidosis reported in the literature Levitt (1941) found 43 cases with ophthalmic symptoms On the basis of these cases he came to the conclusion that sarcoidosis is relatively liable to attack the eye and that any part of the eye or its adnexa may be affected

Up to the 1950s sarcoid iritis was generally called iritis Boeck (Blegvad 1938 Rasmussen 1944 Woods 1949) and the term is still used in the German literature (Wegner & Wurm 1957)

In 1963 Mayock with his coworkers reported on a series of 145 patients with sarcoidosis and compared it with nine materials collected from the literature comprising a total of 1254 cases. Only sufficiently large (28 to 300 patients) histologically confirmed materials comprising clinical manifestations of sarcoidosis of as wide a range as possible had been selected for comparison The frequency of ophthalmic manifestations in these 10 materials averaged 21 % with a range from the 8 7 % of the retrospective study by Ricker & Clark (1949) to the 64 % of the study by Longcope & Freiman (1952) In the latter study special attention had been paid to ophthalmic symptoms In both these studies the vast majority of the patients were Negroes

The work of Longcope & Freiman in the USA was followed by several large histologically confirmed series, with carefully recorded manifestations of sarcoidosis published by the British Crick (1955) James (1956) Ainslie & James (1956) James (1959) Smellie & Hoyle (1960) Crick et al (1961) James et al (1964 1976b) and by the Japanese Yamada et al. (1971)

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In these reports the frequency of ophthalmic changes ranged from 25 % to 63 %

In the Nordic series the frequency of ophthalmic changes ranges from 6 % (Lofgren 1953b, Hannuksela 1971) to 26 % (Nitter 1953 26 %, Gilg 1955 22 % Rulberg-Roos 1962 10 %, Putkonen 1966 15 % Selroos 1969 20 %) In none of these studies had a systematic and detailed examination of the eye been undertaken

The thoroughness of the examination and selection of the material undoubtedly affect the frequency figures for the ophthalmic manifestations in sarcoidosis There may also be considerable geographical differences in the incidence of ocular sarcoidosis This is suggested by the international study of the cases of sarcoidosis in 11 major cities on three continents, carried out by James et al (1976b) The report covered a total of 3676 histologically confirmed cases The frequency of ophthalmic changes ranged in the material from 0 4 % (Naples) to 32 % (Tokyo), with a mean value of 15 % Without biomicroscopy it would not have been possible to record the ophthalmic manifestations in more than an average of 7 %

2 UVEITIS

a GENERAL

In 1909, Schumacher was the first to describe a bilateral nodular iritis with mild symptoms in a female patient aged 42 with Boeck s sarcoid The greyish yellow nodules were situated in the pupillary part of the iris On the basis of the subsequent literature, uveitis is the most common ophthalmic change in sarcoidosis (Woods 1949, Wegner 1957 James et al 1964) A bilateral nodule-producing inflammation of the anterior part of the eye, with mild symptoms and of chronic character has been considered typical (Duke-Elder & Perkins 1966) Usually the nodules heal completely, leaving only a minor scar In a very few cases the uveitis runs a violent course leading to fibrous phthisis some isolated cases have been described by Mylius & Schürmann (1929) Walsh (1939) Woods & Guyton (1944) Crick et al (1961) and James et al (1964) In many series the sarcoid anterior uveitis is far more frequent in women than men (Wegner 1957 James et al 1964 Perkins 1968 Uyama 1972)

Boeck s sarcoid and nodular iritis were generally classified as tuberculosis up to the 1940s (Mylius & Schurmann 1929 Garland & Thompson 1933 Kindt 1940) A tuberculous etiology has had later supporters al (Wegner & Wurm 1957) Blegvad (1938) and Österberg (1939) believed that iris nodules caused by sarcoidosis and tuberculosis could be diffe

rentiated on the basis of their outward appearance In their opinion Boeck s iritis was proliferative in character whereas the tuberculous iritis was more destructive and led to perforation of the eyeball more readily than did sarcoidosis

However, only 1/3—1/4 of the cases of sarcoid uveitis are nodular (Österberg 1939 Crick et al 1961) Perkins (1961) and James et al (1964) divide the arcoid uveitis into a chronic granulomatous and an acute or subacute nonspecific inflammation The latter according to them u ually heals in about six months without leaving any trace

b HEERFORDT S SYNDROME

In 1909 Heerfordt described three patients all with a similar clinical picture uveitis parotitis fever paresis of facial or other cerebrospinal nerves Heerfordt considered the syndrome an atypical form of mump whereas Garland & Thomson (1933) classified it as tuberculous Several other authors of approximately the same epoch concluded that the uveoparotid fever was one of the manifestations of sarcoidosis (Bruins Slot 1936 Waldenstrom 1937 Longcope & Pierson 1937 Pautrier 1938) Al though reports on Heerfordt s syndrome also occur in the more recent literature (Lambert & Richards 1964 Meyer 1973) it has not always been registered as a separate syndrome not even in ophthalmological studies (James et al 1964) According to Crick et al (1961) there was not even one complete Heerfordt s syndrome in their series of 185 patients but only 13 incomplete instance In their series of 388 patients with sarcoid osis Greenberg et al (1964) registered 23 with parotitis eight of whom also had uveitis Perkins (1961) on the other hand found no instance of parotitis among 55 cases of arcoid uveitis

c POSTERIOR UVEITIS

In the earlier literature on sarcoid uveitis the main attention was focused on changes in the anterior segment of the eye (Österberg 1939 Ferguson & Paris 1958) As late as 1964 James and his coworkers carried out an ex tensive study but found only 11 fundus lesions in 123 patients with ocular sarcoidosis They used ophthalmoscopy alone in their examinations as also apparently did Crick and his coworkers in 1961 The latter how ever recorded fundus changes in 30 of their 46 patients with uveitis Gould & Kaufman (1961) found 66 fundus lesions in the literature They analysed the 40 that were sufficiently well documented and paid atten

In these reports the *frequency of ophthalmic changes ranged from* 25 % to 63 %

In the Nordic series, the frequency of ophthalmic changes ranges from 6 % (Lofgren 1953b Hannuksela 1971) to 26 % (Nitter 1953 26 % Gilg 1955 22 %, Rulberg-Roos 1962 10 % Putkonen 1966 15 % Selroos 1969 20 %) *In none of these studies* had a systematic and detailed examination of the eye been undertaken

The thoroughness of the examination and selection of the material undoubtedly affect the frequency figures for the ophthalmic manifestations in sarcoidosis There may also be considerable geographical differences in the incidence of ocular sarcoidosis This is suggested by the international study of the cases of sarcoidosis in 11 major cities on three continents, carried out by James et al (1976b) The report covered a total of 3676 histologically confirmed cases The frequency of ophthalmic changes ranged in the material from 0 4 % (Naples) to 32 % (Tokyo) with a mean value of 15 % Without biomicroscopy it would not have been possible to record the ophthalmic manifestations in more than an average of 7 %

2 UVEITIS

a GENERAL

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Sometimes the nodules occur over small areas only and sometimes they extend throughout the fundus Walsh (1939) was the first to describe the lesion and he as also e g Bruntse (1958) thought that the perivascular location of the lesions was peculiar to the sarcoid change Not all investigators however, have subscribed to this opinion (Woods 1961 Maumenee personal communication cited by Chumbley & Kearns 1972)

Among the cases they collected from the literature Gould & Kaufman (1961) found in 35 % such »candle wax» exudates which have since been recorded by several authors (Geeraets et al 1962 Jutte & Lemke 1965 Chumbley & Kearns 1972 Henkind & Gottlieb 1973 Letocha et al 1975) Turner et al (1975) assumed that the candle wax exudates derived from the vitreous body since in fluorescein fundus angiography they did not leak. Geeraets et al (1962) however were of the opinion that the perivascular location of the lesions and the often non existent vitreous reaction in the eye suggested a chorioretinal origin of the changes

Histological studies of the exudates have been carried out e g by Levitt (1941) MacDonald (1943) Franceschetti & Babel (1949) Tiong (1949) and Gass & Olson (1973) A general observation made by Walsh (1939) Levitt (1941) and Franceschetti & Babel (1949) is that the exudates long remain unchanged sometimes for years They may disappear however rapidly as a result of corticosteroid therapy (Bruntse 1958) and sometimes even spontaneously (Mackensen 1952)

The candle wax exudates are often combined with periphlebitis which was first described by von Bahr (1938) and has later been discussed by e g Wagner (1941) Witmer (1948) and Chumbley & Kearns (1972) According to Gould & Kaufman (1961) periphlebitis occurs in about a half of the eyes with fundus changes The literature contains reports not only on venous changes but also on perivasculitis arteritis and angitis (Jutte & Lemke 1965 Algvere 1970 Uyama 1971) According to Kobayashi (1976) nearly every patient with fundus sarcoidosis exhibits microangiopathy of some degree

Perivasculitis is occasionally connected with a formation of new vessels and retinal and vitreous haemorrhages (Ainslie & James 1956 Quock & Donohoe 1967 François et al 1977) Isolated cases of this type have with the aid of fluorescein fundus angiography been described e g by Shikano & Shimizu (1968) Algvere (1970) Asdourian et al (1975) Letocha et al (1975) Sanders & Shilling (1976) and Madigan et al (1977)

Purely retinal granulomas are rare (Crick et al 1961 Fontan et al 1966) Histologically they have been verified e g by Walsh (1939) MacDonald (1943) Gass & Olson (1973) and Brownstein & Jannotta (1974) The fundus lesions seldom affect the macula but may do so in the form

tion not only to the various types of fundus lesions but also to their frequent association with nervous system symptoms

Since the 1960s fundus changes in sarcoidosis have been systematically sought, with direct ophthalmoscopy supplemented by indirect ophthalmoscopy and three-mirror contact lens Furthermore the type of the lesions has been investigated by means of photography and fluorescein fundus angiography (Jutte & Lemke 1965, Shikano & Shimizu 1968 Yonechi et al 1969 Letocha et al 1975, François et al 1977) It was found that fundus changes are much more common in sarcoidosis than had been believed They are in most cases bilateral and can occur without inflammation of the anterior part of the eye (Gould & Kaufman 1961, Geeraets et al 1962 Chumbley & Kearns 1972, Letocha et al 1975)

According to Gould & Kaufman (1961) the vitreous body is affected in 30 % of the cases of posterior segment sarcoidosis They believe that the vitreous reaction is often characteristic of the disease and like the one first described by Landers (1949) The vitreous lesions at their most typical are light grey, spherical, snowball like formations They vary in size from a small particle to one-third of the optic disc diameter Vitreous opacities have been described e g by Walsh (1939) Crick et al (1961) Jutte & Lemke (1965), and Letocha et al (1975) Histologically, they have been found to be composed of epithelioid and giant cells (Gass & Olson 1973) Landers (1949) thought that they were comparable to the iris nodes of Koeppe (1917) and Busacca (1932) and derived from an inflamed ciliary body an assumption also presented by Crick et al (1961)

Sarcoid chorioretinal lesions were registered by Gould & Kaufman (1961) in up to 40 % of their patients The lesions are similar in appearance to any chorioretinitis The changes may show a scattered location all over the fundus or more often in the lower parts of the fundus (Crick et al 1961 Chumbley & Kearns 1972) Occasionally they are lacking in pigment during the process of scarring (van Heuven 1950 Brewitt & Huerkamp 1976)

Chorioretinal granulomas are rare They may resolve spontaneously (Boke 1961) but they may also progress and necessitate enucleation (Walsh 1939 Franceschetti & Babel 1949)

3 RETINA

The most typical fundus lesions in sarcoidosis are the scattered light coloured, waxlike nodules connected with the veins named »taches de bougie» i e »candle wax» exudates by Franceschetti & Babel (1949)

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of acute neuroretinitis (Ainslie & James 1956, Bruntse 1958) or haemorrhage (Fine & Flocks 1953 Shikano & Shimizu 1968 Letocha et al 1975 Burns 1976)

4 OPTIC NERVE

The optic nerve is affected in 1—5 % of the patients with sarcoidosis (Colover 1948, Blain et al 1965, Laties & Scheie 1970) Of all the cerebral nerves the facial nerve is the only one to be affected more often than the optic nerve Papillitis papilloedema or atrophy of the optic disc are due to uveitis granulomatosis of the optic nerve or intracranial sarcoid infiltration (King 1939, Goldberg & Newell 1944 Colover 1948 Mackensen 1952 Fine & Flocks 1953, Bruntse 1958, Statton et al 1964 Blain et al 1965 James et al 1967, Laties & Scheie 1970, Ingestad & Stigmar 1971, Jampol et al 1972, Chumbley & Kearns 1972 Kelley & Green 1973 Kirkham 1973 Brownstein & Jannotta 1974, Burns 1976 Sanders & Shilling 1976)

5 CONJUNCTIVA

Before the 1930s not more than five cases of conjunctival sarcoidosis had been reported Three of these had been histologically verified (Lutz 1919, Schoeppe 1920 Igersheimer 1925) Adding three new cases to these Blegvad (1931) devoted attention to the morphology, bilateral character and chronic course of conjunctival sarcoidosis In his opinion the typical nodes were yellowish or brownish yellow, of various sizes the largest looking like chalazions and located in the conjunctivae of the tarsus and fornix They produced few symptoms of irritation Sarcoid conjunctival granulomatosis very rarely leads to symblepharon two sporadic instances have been reported (Blegvad 1931 Flach 1978) All Blegvad s patients had skin sarcoidosis and its connection with conjunctival lesions has also subsequently been observed (Krummel 1953)

Many authors claim that conjunctival sarcoidosis is rare (King 1939 Woods 1949 Green & Kennedy 1957 James et al 1964) A world-wide study (James et al 1976b) revealed no conjunctival sarcoidosis among the 542 patients recorded as having ophthalmic manifestations On the other hand special attention has been given to conjunctival sarcoidosis by e g Lindau & Lowegren (1940) Krummel (1953) Bruntse (1958) Zimmerman & Maumenee (1961) Crick et al (1961) Bornstein et al (1962) Karma & Sutinen (1975) and Khan et al (1977) all of whom considered it relatively common

6 LACRIMAL APPARATUS

a LACRIMAL GLAND

In 1934 Savin published a report on 66 cases of uveoparotitis collected from the literature In nine of them the lacrimal gland was enlarged It has later been confirmed by biopsy that bilateral painless lacrimal gland hypertrophy may be a manifestation of sarcoidosis (Rosenbaum 1941 Sniderman 1941 Schultz 1945 Longcope & Freiman 1952 Ainslie & James 1956 Crick et al 1961 Cook et al. 1972) Sarcoidosis of the lacrimal gland can also occur without enlargement of the gland (Crick et al 1961 Green berg et al 1964)

Several authors have remarked on reduced lacrimal secretion in individual cases of ocular sarcoidosis (Gravesen 1942 De Haas 1952 Ainslie & James 1956 Gruber 1956 Jones & Stevenson 1957 Lorentzen 1960) Crick et al (1961) observed as had Jones & Stevenson (1957) that many patients with sarcoidosis complained of a dryness of the eyes and/or mouth in some phase of the disease In the serie reported on by Crick et al (1961) only one patient had a visibly enlarged lacrimal gland whereas lacrimal secretion tested by the Rose Bengal dye was lowered in 66 % The majority of the patients with chronic uveitis had persistent and severe trouble with dry eyes

James et al (1964) found 10 cases of keratoconjunctivitis sicca in a series of 442 patients with sarcoidosis The trouble persisted in six patients Jackson (1970) found that four of his 82 patients with sarcoidosis had enlarged lacrimal glands and approximately half had reduced lacrimal secretion

b LACRIMAL PASSAGES

Watery or bleary eyes in patients with sarcoidosis can sometimes result from granulomatosis in the lacrimal sac and/or ducts This is probably uncommon since only four isolated reports were found in the literature (Lund 1938 Neault & Riley 1970 Fisher et al 1971 Coleman et al 1972)

7 BAND KERATOPATHY AND HYPERCALCAEMIA

Seefelder (1937) was the first to report on the corneal and conjunctival crystal formation in patients with sarcoidosis He considered the lesion to be a complication of uveitis Haldimann (1941) found that the conjunc

of acute neuroretinitis (Ainslie & James 1956, Bruntse 1958) or haemorrhage (Fine & Flocks 1953, Shikano & Shimizu 1968, Letocha et al 1975 Burns 1976)

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nosis of uveitis (Schlaegel 1965 Witmer 1972 James et al 1976a) Others hold the opinion that in chronicised confirmed sarcoid uveitis the Kveim test is not always positive (Siltzbach personal communication cited by Israel et al 1970 Martenet 1972) In a world-wide study of ocular sarcoidosis the Kveim reaction was positive in 80 % of the cases (James et al 1976b)

The suitability of the Kveim test in the diagnosis of uveitis is reduced by the fact that the reaction may be inhibited by systemic corticosteroid therapy which therefore should not be given during the maturation of the test In violent uveitis the consequences may be disastrous to the eye (Crick et al 1961 James et al 1964 Israel 1968)

Because of depression of delayed type hypersensitivity the tuberculin test is often negative in sarcoidosis In Finnish sarcoidosis material however tuberculin positivity is quite frequent (Siltzbach 1967b) perhaps because lung tuberculosis is still common in Finland and nation wide BCG vaccination has been carried out (Selroos 1969) According to Hannuksela & Salo (1969) sarcoidosis is not ruled out until the reaction is positive to 0 01 TU (tuberculin unit)

2 HISTOLOGICAL EXAMINATION OF THE EYEBALL AND OCULAR ADNEXA

Epithelioid cell granulomatosis can occur anywhere in the eyeball or the area of the ocular adnexa (Bruntse 1958 Zimmerman & Maumenee 1961) Comparisons have been made between the ophthalmoscopic and histological changes in the eye by e g Walsh (1939) Witmer (1948) Franceschetti & Babel (1949) and Gass & Olson (1973) In 1975 Thiel & Korenke described a case in which the fundus was ophthalmoscopically normal while histological examination revealed epithelioid cell granulomas in the choroid Histopathological changes in the eyeball have also been reported in sporadic cases by Ohno (1920) Reis & Rothfeld (1931) Landau & Löwegren (1940) Levitt (1941) MacDonald (1943) Woods & Guyton (1944) Rasmussen (1944) Granstrom et al (1946) Tiong (1949) Ricker & Clark (1949) Schimkat (1957) James (1959) and Kelley & Green (1973)

Krummel (1953) was the first to suggest the use of conjunctival biopsy in the diagnosis of sarcoidosis and Crick et al. (1955) described the techniques of the biopsy Despite certain difficulties in differential diagnosis (Crick et al 1961 Zimmerman & Maumenee 1961) and some other drawbacks (Scadding 1967) the conjunctival biopsy being an easy and safe outpatient procedure, forms a useful diagnostic method as a part of the ophthalmological examination (Crick et al 1961 Bornstein et

tival and corneal crystal formation was caused by hypercalcaemia More of these observations have been reported later (Walsh & Howard 1947, Cogan et al 1948, de Haas 1952, Davidson et al 1954, Smith & Hey 1976) However, it has not always been possible to rule out the role of uveitis or reduced lacrimal secretion in the etiology of band keratopathy (Schüpbach & Wernly 1943 Dragstedt & Hjort 1958, O Connor 1972, Lemp & Ralph 1977)

Harrel & Fisher (1939) were the first to draw attention to the elevated serum calcium values of some patients with sarcoidosis In their series of 11 patients six had a serum calcium level exceeding 11 0 mg/100 ml in some phase of the illness Later, many authors have considered hypercalcaemia a rather common complication of sarcoidosis (Longcope & Freiman 1952 Mayock et al 1963, Siltzbach 1967a)

The report published by Goldstein et al (1971), which also contains a comprehensive summary of the reports published earlier, contradicts the assumption of the high rate of hypercalcaemia In their controlled and partly prospective study of 346 patients only eight showed long-term hypercalcaemia The authors draw the conclusion that, thanks to corticosteroids lasting hypercalcaemia has become uncommon It is only associated with the generalised form of severe illness, as observed by Israel (1973) Hypercalcaemia was similarly considered infrequent by Putkonen et al (1965), who in their controlled series of 60 patients observed transient hypercalcaemia in only two patients while hypercalciuria was no more frequent than in the control subjects

B Ophthalmological aspects in diagnosing sarcoidosis

1 GENERAL

The diagnosis of sarcoidosis is based on clinico-radiographic findings and on histological evidence obtained by tissue biopsy or a positive Kveim test (Kveim 1941) Certain immunological and enzymological peculiarities also play an important part in the diagnosis of the disease (James et al 1975 Horsmanheimo & Fudenberg 1977 Goldstein et al 1978 Selroos 1978)

The Kveim test has not achieved an undisputed position as a routine procedure since it has not been possible to produce any standardised antigen for general use and its specificity is still in question (Israel 1974) The role of the test is of course stressed whenever no histological specimen is available It is recommended by many for use in the diag-

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c IRIS INFRARED TRANSILLUMINATION PHOTOGRAPHY

The iris infrared transillumination method for elucidation of iris structures was developed at the Ophthalmological Clinic of Oulu University Central Hospital (Saari et al 1977) The method reveals details in the deeper layers of the iris better than the transillumination alone since the pigment epithelium forms a barrier to the transmission of visible light while infrared photography alone shows only the superficial layer of the iris (Matthaus & Grotzsch 1966)

No reports on the use of the iris infrared transillumination method in the examination of ocular sarcoidosis were found in the literature

al 1962, Karma & Sutinen 1975) Positive findings are most frequently seen in the active generalised form of the disease (Bornstein et al 1962 Karma & Sutinen 1975)

3 PHOTOGRAPHIC METHODS

a FLUORESCEIN FUNDUS ANGIOGRAPHY

In 1968 Shikano & Shimizu described the first fluorescein angiographic findings in patients with sarcoidosis In their cases the changes were restricted to the vessels of the retina In the authors opinion, they resembled the angiographic changes seen in an old central vein thrombosis or Behçet s disease The nature and course of sarcoid fundus changes have subsequently been studied e g by Chumbley & Kearns (1972) and Letocha et al (1975) In these works periphlebitis was the most common finding Kobayashi (1976) carried out fluorescein fundus angiographies on 13 of his 47 patients with ocular sarcoidosis In all of the 13 cases an increased permeability was observed both in the veins and in the arteries Microangiopathy of some degree was seen in 90 % of all the 47 cases Algvere (1970) also found arterial as well as venous changes and neovascularisation similar to that seen in Eales disease Peripheral retinal neovascularisations have also been studied by fluorescein angiography by Asdourian et al (1975), Madigan et al (1975) and Sanders & Shilling (1976)

Chumbley & Kearns (1972) and Sanders & Shilling (1976) described the hyperfluorescence of sarcoid optic disc oedema Sarcoid granulomatosis of the optic disc has by some investigators been found to leak fluorescein (Kojima et al 1969 Kirkham 1973) and by others not to leak fluorescein (Jampol et al 1972) In the series of 10 patients reported by Letocha et al (1975) one patient had a chorioretinal granuloma showing initial hypo- and late hyperfluorescence A similar case was also described by Turner et al (1975)

b FLUORESCEIN IRIS ANGIOGRAPHY

Fluorescein iris angiographic studies on changes in the vascular pattern of the iris caused by uveitis have been reported by e g Cobb & Smith (1970) Demeler (1978) and Laatikainen (1979) and two tuberculomas have been revealed by angiographic studies of the iris (Nieuwenhuis 1976 Kottow 1977) No references were found in the literature to sarcoid granulomatosis examined by angiography of the iris

ture showing productive epithelioid cell granulomatosis without necrosis or with slight fibrinoid necro is was accepted as representing sarcoidosis However cases that were histologically positive and therefore suspect but in which there was otherwise no sign of systemic disease were not included in the series In these cases a local sarcoid reaction may have been involved

The Kveim test was carried out on 20 patients with Finnish antigen and was positive in 15

The tuberculin test was made with purified protein derivative PPD RT23 (Statens Seruminstitut Copenhagen) using the concentration of 1 TU/0 1 ml* If the result was negative the test was repeated with a concentration of 10 TU/0 1 ml If the result was still negative a small number of patients were re tested with a concentration of 100 TU/0 1 ml The test was assessed as positive if after 48 hours the site of injection showed an elevated red induration 10 mm in diameter The results of the tuberculin test are shown in Table III

In regard to differential diagnosis between sarcoidosis and tuberculosis the following findings were of importance a repeatedly negative sputum culture the often spontaneous regression of lung changes ineffectiveness of antituberculous treatment given in some cases and a favourable response to corticosteroid treatment If the sputum sample even once showed a tubercle bacillus on microscopy or culture the case was excluded from the series despite hi tological clinical and/or radiological evidence of sarcoidosis

The serum calcium was determined by atomic absorption spectrophotometer (Varian Techtron AA5) and since 1975 by calcium analyser (Corning 940) 2 2—2 6 mM/l was taken to be the normal range

The small bones of the hands and feet of 219 patients were x rayed The roentgenographs were reviewed by a radiologist using the criteria of Neville et al (1976) in the classification of the sarcoid changes

After the diagnosis the patient s condition was followed up at regular intervals (3—6 months) at the Oulu University Central Hospital the Paivarinne Hospital or in mild cases at the local tuberculosis dispensaries

B Patients

The series comprised 281 patients with sarcoidosis The patients lived in the Counties of Oulu and Lapland within the area (A B C) marked on the attached map (Fig 1) with a total population of c 600 000

1 TU (tuberculin unit) = 0 00002 mg purified protein derivative (PPD)

III MATERIAL AND METHODS

A Diagnosis of sarcoidosis

During the years covered by the present study, 1971—1977 all the patients in whom (a) chest radiography revealed a finding suggesting sarcoidosis, or (b) a possible sarcoid manifestation was discovered in medical examination, were referred to the Oulu University Central Hospital or the Paivarinne Hospital, which is a hospital for lung and internal diseases for a detailed examination to confirm the diagnosis

The diagnosis of sarcoidosis was made on the basis of typical clinico-radiological findings and verified histologically in every case The clinico-radiological picture considered typical of sarcoidosis consisted of hypertrophy of hilar glands symptom-free or with mild general symptoms, possibly associated with pulmonary infiltration A physician specialised in pulmonary diseases and interested in sarcoidosis reviewed all the chest radiographs The findings were classified as follows (Wurm et al 1958)

0° = no sarcoid changes
I° = bilateral hilar lymphadenopathy (BHL) polycyclic hilar gland enlargements occasionally enlargement of other mediastinal or paratracheal glands
II° = perihilar miliary or nodular parenchymal infiltration in addition to or without BHL
III° = irreversible fibrotic changes

In a number of patients the pulmonary finding was accompanied by an additional extrathoracic sarcoid change erythema nodosum cutaneous lesion peripheral lymphadenopathy an ophthalmological neurological or parotid manifestation

The biopsy for histological verification was obtained by mediastinoscopy in 254 cases and in the remaining cases from the liver a peripheral lymph node the skin bronchial mucosa or tonsil In 64 cases a positive finding was obtained from two or more sites A histological pic-

ture showing productive epithelioid cell granulomatosis without necrosis or with slight fibrinoid necrosis was accepted as representing sarcoidosis However cases that were histologically positive and therefore suspect but in which there was otherwise no sign of systemic disease were not included in the series In these cases a local sarcoid reaction may have been involved

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TABLE I

Distribution of the patients by year of onset

Year	N	%
1955—1969	25	8 9
1970	26	9 2
1971	44	1 7
1972	38	13 5
1973	39	13 9
1974	28	10 0
1975	27	9 6
1976	29	10 3
1977	25	8 9
Total	281	100 0

sarcoidosis still produced symptoms requiring examination or treatment The distribution of the series by the year of onset is shown in Table I

The annual incidence of sarcoidosis could be calculated in the Tuberculosis District of North Ostrobothnia (Fig 1) since all the new cases of sarcoidosis diagnosed within this district in 1971—1977 were included in the present material During this period the mean population in the Tuberculosis District of North Ostrobothnia was 286 126 (Official Statistics of Finland 1978) and the average number of new cases of sarcoidosis diagnosed annually was 29 5 Hence the annual incidence of sarcoidosis in this district was 10 3 per 100 000 of population

Of the 281 patients of the series 163 (58 %) were women and 118 (42 %) men The age of onset ranged from 15 to 70 years average 36 6 years The onset was most frequent in age group 25—34 years (Table II)

TABLE II

Age of onset and sex distribution

Age (years)	Female	%	Male	%	Total	%
15—24	10	6 2	16	13 6	26	9 3
5—34	47	8 8	66	55 9	113	40 2
35—44	49	30 1	5	1 2	74	26 3
45—54	39	23 9	10	8 5	49	17 4
55—64	15	9 2	1	0 8	16	5 7
≥ 65	3	1 8	0	0 0	3	1 1
Total	163	100 0	118	100 0	281	100 0

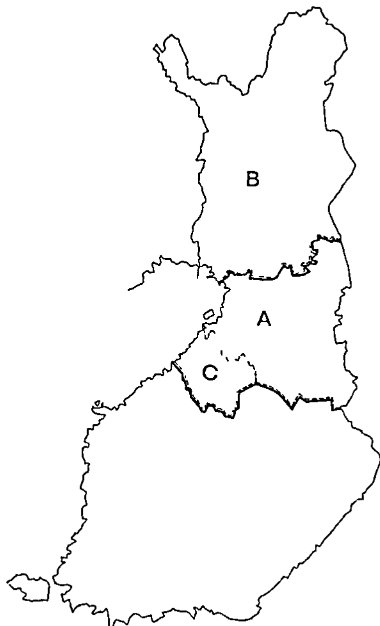


Fig 1 The patients lived in the Counties of Oulu and Lapland which comprised three tuberculosis districts (A) North Ostrobothnia (B) Lapland and (C) Central Ostrobothnia

The onset of illness was determined to have taken place in the year when the lesion which subsequently proved to be sarcoidosis was first discovered by the examining physician In addition to new case the series contained 25 patients who had fallen ill prior to 1970 but whose

The age of onset was different for men and women Men constituted the majority among patients under 35 years of age This group comprised c 70 % of all the men After the age of 35 the ratio was reversed and 65 % of all the women belonged to this group

The general clinical feature of the series are presented in Table III In 124 cases the disease was registered with pulmonary changes alone Of these patients only 39 had noticed mild general symptoms while 85 subjects were symptom free and the sarcoidosis had been revealed by routine chest radiography 157 had also extrathoracic symptoms many of them several

The second most common extrathoracic manifestation after ophthalmic changes was erythema nodosum (EN) in 66 cases (23 5 %) 55 women and 11 men In the acute stage of EN 34 patients had pain and swelling in the joints which subsided when the EN nodes disappeared Of the 66 subjects whose illness began with EN 58 could indicate the month of onset for 37 of them it was February May Forty-two patients (14 9 %) reported pain and other symptoms in the major joints apparently due to sarcoidosis but without erythema nodosum

Sarcoid skin changes were observed in 35 cases (12 4 %) nodular infiltrations plaques lupus pernio or scar reactions Thirty four of these were confirmed histologically Parotid swelling lasting a few weeks to a couple of months was noted in 13 including two with transient facial palsy Eighteen of the subjects developed neurological symptoms facial palsy was the only one in 6 Three had both facial palsy and other nervous system symptoms

B lateral hilar lymphadenopathy (BHL) or I° change was the most common radiological intrathoracic finding in 163 patients (58 0 %) As mentioned before it was often revealed unexpectedly by a mass x ray survey This change was seen in 55 % of the men and 36 % of the women A II pulmonary change at the time of onset was recorded in 96 (34 2 %) and III pulmonary change in 18 (6 4 %) of the patients included in the present series Four subjects whose sarcoidosis had extrathoracic manifestations had at the onset, no radiological pulmonary changes compatible with this disease Two of them were subjected to mediastinoscopy and one showed a histological change compatible with sarcoidosis in mediastinal lymph nodes *

After completion of the study one of the four patients (Case 6 Table X) developed a radiologically detectable sarcoid change which was confirmed by mediastinal lymph node biopsy 3 1/2 years after the first symptoms of the d sease

TABLE III

The clinical picture of 281 patients with sarcoidosis

	N	%
Sex		
Female	163	58.0
Male	118	42.0
Age (years)		
Under 40	181	64.4
Over 40	100	35.6
Manifestations		
Only intrathoracic involvement	124	44.1
Symptom-free	85	30.2
Extrathoracic involvement	157	55.9
EN with or without joint symptoms	66	23.5
Cutaneous lesions	35	12.4
Joint symptoms without EN	42	14.9
Peripheral lymphadenopathy	16	5.7
Parotid enlargement	13	4.6
Nervous system symptoms	18	6.4
Facial palsy	9	3.2
Bone changes [1]	7	3.2
Hypercalcaemia [2]	16	7.2
Ophthalmic changes	79	28.1
Chest radiograph at the time of onset		
0°	4	1.4
I°	163	58.0
II°	96	34.2
III°	18	6.4
Results of tuberculin test		
1 TU [3] negative	226	84.0
positive	43	16.0
10 TU [4] negative	114	59.7
positive	77	40.3
100 TU [5] negative	29	61.7
positive	18	38.3

[1] 219 patients examined
[2] 222 » »
[3] 269 » »
[4] 191 »
[5] 47 »

comprising 113 patients i.e. 40 % of the total material. After the age of 40 the number of new cases of sarcoidosis fell considerably and only 7 subjects acquired the disease after the age of 60. Similarly patients under 20 were few: the age group 15—19 contained only five subjects.

of the field of vision with Friedmann's perimeter with due regard t
refraction and age correction

The slit lamp examination was made with Haag Streit's biomicroscope
The intraocular pressure was measured with applanation tonomete
(Haag Streit) The pupils were dilated with 0 5 % tropicamide 5 %
methaoxedrine and if necessary with 10 % methaoxedrine After maxima
dilatation the lens and the anterior vitreous were examined The fundu
was examined with direct ophthalmoscopy Subsequently Goldmann
three-mirror contact lens was used to examine the chamber angle vit
reous and fundus to the extreme periphery

The classification of uveitis into granulomatous and nongranulomatou
was based on the criteria of Hogan et al (1959) and Kimura et al (1959)
and into acute and chronic on the criteria of Woods (1961) (see page
32—33 for details)

The region of the lacrimal gland was palpated Lacrimal gland func
tion was ascertained with Schirmer's test (Schirmer 1903) after examin
ation of the vision and preliminary biomicroscopy A 35 mm long Schirme
test strip (developed and standardised by G Peter Halberg M D an
Conrad Berens M D N Y City) folded to angle at the 5 mm mark wa
placed underneath the outer half of the lower lid without preceding loc
anaesthesia The moistened length of the test paper was measured afte
5 min The lacrimal secretion was assessed as normal if the moistene
length exceeded 16 mm and pathological if the result was ≤ 7 mm I
the latter event the test was immediately repeated twice The cases i
which the moistened length was 8—15 mm were re-examined by repeatin
Schirmer's test and by biomicroscopy of the lacrimal film

The Rose-Bengal test (1 % dichloro-tetraiodo fluorescein sodium so
ution) was performed in uncertain cases on 36 patients at re-examinatio
The result of the test was assessed according to the staining schedu
proposed by Holm (1949) in which the staining intensity was divide
into three categories In the most severe cases the bulbar conjuncti
stained intensely triangularly from its palpebral area as did the low
corneal segment In the mildest cases the staining of the conjunctiva ar
cornea was discontinuous and minor stained particles were seen on th
palpebral fissure area of the conjunctiva and in the lower parts of th
cornea

Any calcium deposits of the conjunctiva were registered and a clo
watch was kept for band keratopathy taking care not to confuse it wi
the white-limbus girdle phenomenon (Sugar & Kobernick 1960) or th
small marginal crystals which are often seen without known reason o
pathological significance (Cogan et al 1948) The serum calcium valu

C Ophthalmological examination

In every case the eyes were examined at least once, and in many cases several times by the author herself The examinations were usually carried out in the outpatient clinic Only the cases of uveitis requiring hospitalisation were examined in the inpatient wards The interval from manifestation of the disease to the first ophthalmological examination was, on average, 5 5 months (Table IV)

The patient s ophthalmological history was recorded Special attention was given to symptoms possibly associated with sarcoidosis such as those of iritis dryness or possible enlargement of the lacrimal gland An effort was also made to record the history of other earlier manifestations and symptoms of sarcoidosis

During the period 1971—1974 the programme included a determination of visual acuity, slit lamp examination, measurement of intraocular pressure direct ophthalmoscopy and examination of the fundus with three mirror contact lens In September 1974 a neuro-ophthalmological examination study of the lacrimal gland function and conjunctival biopsy were added The 144 patients examined before September 1974 were invited for re-examination in order to obtain identical data on the status in every case Despite repeated invitations 25 patients failed to attend Hence 25 (8 9 %) of the series were not so fully examined as the remaining 91 1 %

Visual acuity with appropriate correction was examined with Snellen s E chart, and the result was expressed with decimals The neuro ophthalmological examination consisted of the following ocular movements cover test pupillary reflexes sensibility of the cornea and determination

TABLE IV

Interval from manifestation of the disease to the first ophthalmological examination

Interval months/years	N	%
< 1 mo	9	3 2
1— »	73	26 0
3— mos	68	24 2
6— »	50	17 8
1— yr	30	10 7
2— yrs	14	5 0
4— »	18	6 4
≥ 6 »	19	6 7
Total	281	100 0

camera attached to a Zeiss biomicroscope on a Kodak high-speed infrared black and white film while two Zeiss cameras were used for stereophotography

E Conjunctival biopsy

Conjunctival biopsy was taken on average 6—12 months and exceptionally up to 25 years after the onset of the symptom leading to a diagnosis of sarcoidosis The procedure for which the patient s consent was obtained was carried out in an outpatient clinic after the ophthalmological examination (Crick et al 1955 Karma & Sutinen 1975) Under superficial anaesthesia (0 4 % oxybuprocaine) and under the control of an operation microscope 1—2 follicles if seen were removed by forceps and scissors from the lower fornix or the conjunctiva of the lower lid tarsus if no follicles were seen an excision of 3—4 sq mm was made in the conjunctival mucosa

The specimen was fixed in formalin and embedded in paraffin To start with (the first 136 biopsies) only few (2—12) sections were cut from the specimen and the balance was serially sectioned at 6 μ spacing if possible The sections were stained with haematoxylin eosin (H E) The author personally together with the same histopathologist familiar with sarcoidosis examined all the specimens

To study the interconnection between the histological conjunctival finding and the trend of the process seen from chest radiographs the patient s lungs were x rayed at the time of the conjunctival biopsy if more than two months had elapsed from the preceding lung radiography The possible differences between sarcoid changes observed from the radiographs were described as follows the changes had disappeared were as before showed progression but no fibrosis regression without fibrosis progression and fibrosis regression and fibrosis

A control series for the conjunctival biopsy consisted of 40 subjects with no sarcoidosis admitted to the ophthalmological ward for strabismus or cataract age range 20—60 years

F Statistical analysis

The Oulu University Computer Centre was responsible for the processing of the data The computer was a Univac 1100/20 and the programme used was HYLPS The significance of the differences found was studied with the chi square test and determined as follows $p < 0.05$ was almost significant $p < 0.01$ was significant and $p < 0.001$ was highly significant

was determined in connection with the ophthalmological examination if the interval from the former determination exceeded two months

Between the periods of hospital treatment, the patients with uveitis were followed up at regular intervals of 1—3 months until the uveitis subsided In addition, nearly all the patients in whom the first ophthalmological examinations had revealed *some other sarcoid ophthalmic* lesion, were re-examined at least once and generally many times during the years covered by the present study, until the lesion had disappeared or ceased to progress Furthermore those patients with sarcoidosis who at the follow-ups at the medical outpatient clinic, complained of eye trouble — a total of 25 — were referred for ophthalmological examination

D Photographic methods

Fluorescein fundus angiography Seven fundus angiographies were carried out on five patients with uveitis two of whom were examined twice A Robot camera attached to the Zeiss fundus camera was used The excitation filter was Baird Atomic B4, the barrier filter Kodak Wratten 15 and the film Kodak Tri-X-Pan The contrast medium used was 10 % sodium fluorescein 0 043 ml/kg It was rapidly injected through an intravenous cannula, followed immediately by 5 ml physiological saline The 0 picture was taken before the injection angiography started 5—10 sec after the contrast medium had been injected and serial photography took place at 0 8 sec intervals

Fluorescein iris angiography Uni- or bilateral iris angiography was performed on 10 patients with uveitis on many of them several times In unilateral angiography the equipment consisted of a Zeiss biomicroscope to which a motor-driven Nikon camera was attached The filters were the same as above A time-counter was connected to the system Otherwise the procedure and speed were identical to those in fluorescein fundus angiography

For bilateral iris angiography two Nikon cameras were connected to the system By means of prisms both irides could be photographed simultaneously (Helve & Nieminen 1974)

Iris infrared transillumination photography Iris infrared transillumination mono- or stereophotography was carried out on a total of 16 patients with uveitis on some of them several times The light was directed via the lateral wall of the eyeball through optic glass fibre and Kodak Wratten No 87 filter The mono pictures were taken with a Zeiss

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TABLE VI

Ophthalmic symptoms and their duration at the time of the first examination

Ophthalmic change	Total	No symptoms	Symptoms during < 1 mo	< 3 mos	< 6 mos	< 1 year	>
Histologically verified conjunctival granuloma	37	33		2		1	1
Reduced lacrimal secretion	3[illegible]	[illegible]0		3	3	1	5
Uveitis	22	5	3	7	3	3	1
Band keratopathy	11	9	1	1			
Enlarged lacrimal gland	6	3			2	1	
Episcleritis	5		2	3			
Dacryostenosis	5						5
Fundus change without diagnosed uveitis	3	2					1
Total	121	7[illegible]					

IV RESULTS

A General

1 FREQUENCY AND SYMPTOMS OF OPHTHALMIC CHANGES

One or more ophthalmic manifestations of sarcoidosis were detected in 79 patients (28.1 % of the total series) (Table V)

Sarcoidosis of the conjunctivae and reduced lacrimal secretion were the most frequent of the ophthalmic changes 17.0 % and 12.6 % respectively, while uveitis ranked third with 7.8 % Conjunctival sarcoidosis was a *significantly* ($p < 0.01$) *more* common finding than uveitis The difference between frequencies of reduced lacrimal secretion and uveitis was not statistically significant

In 12 of the 281 patients the ophthalmic symptoms dominated the picture (11 cases of uveitis and one conjunctival granulomatosis) Twenty-five patients presented milder and transient symptoms requiring examina-

TABLE V

Primary ophthalmic changes in 79 patients

Ophthalmic change	N	% of all the patients examined
Histologically verified conjunctival granuloma	37	17.0 [1]
Reduced lacrimal secretion	32	12.6
Uveitis	22	7.8
Band keratopathy	11	3.9
Enlarged lacrimal gland	6	2.1
Episcleritis	5	1.8
Dacryostenosis	5	1.8
Fundus change without diagnosed uveitis	3	1.1

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Band keratopathy	11	9	1	1			
Enlarged lacrimal gland	6	3			2	1	
Episcleritis	5		2	3			
Dacryostenosis	5						5
Fundus change without diagnosed uveitis	3	2					1
Total	121	72					

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Fundus change without diagnosed uveitis	3	1 1

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* 254 »

TABLE VIII

Coexistence of ophthalmic and other sarcoid changes.

Ophthalmic change		Other change												
		Chest at onset				EN	Skin	Joints	Periph lymph	Par otid	Facial palsy	Other neurol	Bones	Hyper calc
		0	I°	II	III°									
	Total	4	163	96	18	66	35	4?	16	13	9	1˷	7	16
Histologically verified conjunctival granuloma	37	0/3	12/121	19/80	6/14	8/49	1?/33	6/34	3/1?	3/12	1	3 9	0/4	5/10
Reduced lacrimal secretion	3?	1/3	15/145	13/90	3/16	5/59	15/34	8/36	5/12	6/12	4	6/11	1	8/14
Uveitis	22	2	10	10	0	4	7	6	4	3	4	5	0	4
Band *keratopathy*	11	0/3	?/147	8/90	1/16	4/5?	4/?8	2/33	3/13	1/10	0/7	?/10	1 6	7
Enlarged lacrimal gland	6	1	1	3	1	1	5	2	1	4	1	3	0	0
Episcleritis	5	0	4	1	0	4	1	0	0	0	0	0	0	0
Dacryostenosis	5	0	?	1	2	2	2	1	2	1	1	0	0	1
Fundus change without diagnosed uveitis	3	0	1	2	0	0	2	2	1	0	0	0	0	1

The denominator is given whenever the number of examined cases with an isolated ophthalmic change differs from the total of other changes

tion by an ophthalmologist at some stage of the disease Table VI describes the number and symptoms of the various ophthalmic lesions at the time of the first ophthalmological examination, and their duration prior to it *Seventy-two of 121 sarcoid eye affections produced no symptoms at all* the figure includes five cases of uveitis that were undetected until revealed by the slit-lamp examination Thirty-two patients had reduced lacrimal secretion which in only 12 cases had given rise to symptoms Of the 37 patients with conjunctival sarcoidosis only four had symptoms which in one patient were really pronounced

2 COEXISTENCE WITH OTHER SARCOID CHANGES

Ophthalmic changes were seldom seen without other extrathoracic manifestations of sarcoidosis (Table VII) However conjunctival sarcoidosis was found to be the only extrathoracic sign of the disease in 15 of 37 cases, while decreased lacrimal secretion was the only sign in seven of 32 cases

Table VIII shows how many and what type of other manifestations of sarcoidosis were detected in connection with the various ophthalmic changes and Table IX presents the number of patients with coexistence of ophthalmic and other sarcoid manifestations 33 % of the patients with

TABLE VII

Number of other extrathoracic manifestations accompanying the various ophthalmic findings

Ophthalmic change	Total	Other extrathoracic change	
		Yes	No
Histologically verified conjunctival granuloma	37	22	15
Reduced lacrimal secretion	32	25	7
Uveitis	22	19	3
Band keratopathy	11	10	1
Enlarged lacrimal gland	6	5	1
Episcleritis	5	5	0
Dacryostenosis	5	5	0
Fundus change without diagnosed uveitis	3	2	1
Total	121	93	28

TABLE VIII

Coexistence of ophthalmic and other sarcoid changes

Ophthalmic change	Total	Chest at onset 0	I°	II	III	EN	Skin	Joints	Periph lymph	Parotid	Facial palsy	Other neurol	Bones	Hyper calc
						Other change								
Total		4	163	96	18	66	35	4?	16	13	9	12	7	16
Histologically verified conjunctival granuloma	*37*	*0/3*	1_/1 1	19 80	6/14	8/49	1?/33	6/34	3/1?	3/12	1	3/9	0/4	5/10
Reduced *lacrimal* secretion	3?	1/3	15/145	13/90	3/16	5/59	15/34	8/36	5/12	6/12	4	6/11	1	8/14
Uveitis	2	2	10	10	0	4	7	6	4	3	4	5	0	4
Band keratopathy	11	0/3	2/147	8/90	1/16	4/5	4/?8	2/33	3/13	1/10	0/7	_/10	1 6	7
Enlarged *lacrimal* gland	6	1	1	3	1	1	5	2	1	4	1	3	0	0
Episcleritis	5	0	4	1	0	4	1	0	0	0	0	0	0	0
Dacryostenosis	5	0	2	1	-	2	2	1	-	1	1	0	0	1
Fundus change without *diagnosed uveitis*	3	0	1	?	0	0	2	2	1	0	0	0	0	1

The denominator is given whenever the number of examined cases with an isolated ophthalmic change differs from the total *of other changes*

tion by an ophthalmologist at some stage of the disease Table VI describes the number and symptoms of the various ophthalmic lesions at the time of the first ophthalmological examination, and their duration prior to it *Seventy-two of 121 sarcoid eye affections produced no symptoms at all*, the figure includes five cases of uveitis that were undetected until revealed by the slit-lamp examination Thirty-two patients had reduced lacrimal secretion which in only 12 cases had given rise to symptoms Of the 37 patients with conjunctival sarcoidosis, only four had symptoms which in one patient were really pronounced

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Episcleritis	5	5	0
Dacryostenosis	5	5	0
Fundus change without diagnosed uveitis	3	2	1
Total	121	93	28

intraocular pressure up to 50 mmHg which produced symptoms of pain and dimming of the vision In all the other cases the symptoms were milder slight photophobia reddening and gradual reduction of vision or floating flakes in the field of vision It could take months or even a year before the patient consulted a doctor for examination and treatment (Table VI)

The cases in which one or more of the following changes were seen in some phase of the disease were classified as granulomatous fatty precipitates iris nodules snowball opacities in the vitreous retinal and optic disc granulomas taches de bougie exudates or chorioretinitis changes As a result 17 cases of uveitis were considered granulomatous and five non granulomatous (Tables X and XI) In four cases in which the course of the disease was classified as acute biomicroscopy revealed signs of uveitis compatible with a granulomatous process All the 13 cases of uveitis with a chronic course were classified as granulomatous (Table XI) Uveitis was classified as bilateral when it occurred simultaneously in both eyes Twenty of the 22 cases of uveitis were bilateral

There was a difference though not statistically significant ($0.05 < p < 0.1$ $\chi^2 = 3.63$) in sex distribution 17 women and five men

Sarcoid uveitis occurred in all age groups apart from that of over 65 and the mean age was 40.3 years (Table XII) The share of the chronic form increased although not significantly after the age of 45

The association between uveitis and the non-ophthalmic manifestations of sarcoidosis is shown in Table XIII Three of the 13 subjects with chronic uveitis showed no sarcoid pulmonary change at the onset but two developed them (Cases 1 and 6 Table X) within 10 and 3 1/2 years of the onset of uveitis A I change in chest radiograph was detected in seven of the nine patients with acute and three of the 13 with chronic uveitis In acute uveitis the lung lesions were resolved in less than two years in the chronic they remained unchanged A II lung lesion was seen in two of the nine patients with acute and nine of the 13 with chronic uveitis None of these developed signs of pulmonary fibrosis during the period of the present study

In two patients with acute and one with chronic uveitis no other extrathoracic manifestations were detected In all the other patients extrathoracic manifestations were present an average of 1.9 per patient with chronic uveitis and 1.3 per patient with the acute form All cases of uveitis associated with hypercalcaemia were chronic Those with chronic uveitis displayed more other ophthalmic changes than those with the acute form 1.2 and 0.7 per patient respectively (Table XIV)

TABLE IX

Coexistence of other sarcoid and ophthalmic changes

Other change	Patients N	Patients %	Patients with ophthalmic changes N	Patients with ophthalmic changes %
Intrathoracic involvement	279	99.3	78	28.2
Erythema nodosum	66	23.5	22	33.3
Skin changes	35	12.4	23	65.7
Joint symptoms	42	14.9	19	45.2
Peripheral lymphadenopathy	16	5.7	11	68.7
Parotid enlargement	13	4.6	8	61.5
Facial palsy	9	3.2	6	66.7
Other nervous system symptoms	12	4.3	8	66.7
Bone changes	7	3.2	1	14.2
Hypercalcaemia	16	7.2	12	75.0

erythema nodosum showed ophthalmic changes More ophthalmic changes were shown by patients with joint, parotid or neurologic affections, and significantly more ($P < 0.01$) by patients with sarcoid changes in the skin, peripheral lymphadenopathy or hypercalcaemia

B Ophthalmological findings in detail

1 UVEITIS

a CLASSIFICATION

The series contained a total of 22 patients with uveitis (7.8 %) According to the course of the disease the cases were divided into acute and chronic on the one hand and according to their biomicroscopical appearance into granulomatous and non granulomatous on the other as shown in Tables X and XI Cases with a more or less sudden onset and remission within six months not recurring during the years covered by the present study were classified as acute A case was considered chronic if the inflammation continued silently for years and finally subsided or if phases of exacerbation followed one after the other

On this basis nine of the cases were classified as acute and 13 as chronic In five cases the onset of uveitis was accompanied by a rise in

Hypopyon	Vitreous cell opacities	Snowball opacities	Macular oedema	Optic nerve changes	Chorioretinitis	Diffuse periphlebitis	Taches de bougie exudates	Retinal haemorrhages	Retinal granulomas	Retinal detachment	Clinical classification
	+		++						+		Chronic granulomatous
	+										Acute non granulomatous
	++	+			+						Chronic granulomatous
	++				+						Chronic granulomatous
	+		+				+				Chronic granulomatous
	+	++	+	+	++	+	+		+		Chronic granulomatous
	+										Acute non granulomatous
				+			+				Acute granulomatous
	+			+	+						Chronic granulomatous
	+	+					+				Acute granulomatous
	+	+				+	+				Chronic granulomatous
											Acute non granulomatous
	+	+			++	+					Chronic granulomatous
				+	+	+	+				Acute granulomatous
	+										Acute non granulomatous
	+	+				+	+	+		+	Chronic granulomatous
	+	+					+				Chronic granulomatous
					+		+				Chronic granulomatous
	+	+									Chronic granulomatous
											Acute non granulomatous
	+	+					+	+			Chronic granulomatous
	+										Acute granulomatous

TABLE X

Synopsis of the findings in uveitis during an average 4 1/2 years of follow up

Only positive findings have been entered

Case no	Age	Sex	Symptoms of uveitis before diagnosis	Follow up time (years)	Monocular	Binocular	Latest visual acuity (R/L)	Band keratopathy	Small keratitic precipitates	Mutton-fat keratitic precipitates	Aqueous flare	Aqueous cells	Iris nodules	Iris atrophy	[illegible]
1	34	F	1 mo	10	+		0 7/CF		+		++	+		+	
2	62	F	NO	1/2		+	1 4/1 4		+		+	+			
3	59	F	9 mo	4		+	1 4/CF	+		+	+	+	++	+	
4	19	M	2 mo	3		+	0 7/0			++	++	+	++	++	-
5	24	F	2 ye	4		+	1 2/0 9		+		+	+			
6	42	F	4	4	+		1 2/1 1		+	+	+	+	++	+	
7	27	M	2 ye	7		+	1 4/1 4				+	+			
8	38	M	1 mo	1		+	1 4/2 0			+	++	+			
9	39	F	1 mo	7		+	1 4/1 4	++			+	+		+	
10	42	F	2 mo	4		+	1 4/1 4			++	++	++	++	+	
11	32	F	8 mo	5		+	1 2 0 7	++		++	+	+		+	
12	27	F	1 mo	3		+	1 6/1 6		+		+	+			
13	64	F	3 mo	5		+	CF/0 3				+	+		+	
14	40	M	3	11		+	1 6/1 2		+		+	+		+	
15	53	F	NO	2		+	1 2/1 1		+		+	+			
16	48	F	11 mo	4		+	0 4/1 0		+	+	+	+			
17	23	M	2	3		+	1 4/1 4	+	+	+	+	+	+	+	
18	40	F	NO	4		+	1 0/0 9		+		+	+			
19	52	F	1 mo	7		+	0 9 0 9		+		++	+			
20	32	F	NO	2		+	1 6/1 6		+		+	+		+	
21	52	F	NO	5		+	1 4/1 4		+		+	+		+	
22	37	F	2 mo	4		+	CF/CF			++	++	++			

* + = *positive finding* ++ = *highly positive finding*

CF = counting fingers

TABLF XIII

The non-ophthalmic m nife (itions of arcoidosis in uveitis

Uveitis	Total	Intra thoracic	EN	Skin	Joints	Periph lymph	Parotid	Facial pal y	Other neurol	Bones	Hyper calc	Tot il
Acute	9	9	1	3		-	1	1	2	0	0	1
Chronic	13	1	3	4	4		2	3	3	0	4	37
Total		1	4	7	6	4	3	4	5	0	4	58

TABLE XIV

Other ophthalmic manifest itions of sarcoidosis in uveitis

Uveitis	Total	Histologically verified conjunctival granuloma	Reduced lacrimal secretion	Enlarged lacrimal gland	Dacryo stenosis	Band keratopathy	Total
		37	3	6	5	11	91
Acute	9	1	4	1	0	0	6
Chronic	13	4	6	1	1	4	16
Total	2-	5	10	2	1	4	2?

TABLE XI

Clinical classification of uveitis

	Acute	Chronic	Total
Granulomatous	4	13	17
Non granulomatous	5	0	5
Total	9	13	22

TABLE XII

Age distribution in uveitis

Age	Acute uveitis (men)		Chronic uveitis (men)		Proportion of age group	%
15—24	0		3	(2)	3/26	12
25—34	3	(1)	2		5/113	4
35—44	4	(2)	3		7/74	9
45—54	1		3		4/49	8
55—64	1		2		3/16	19
≧ 65	0		0		0/3	0
Total	9		13			

b HEERFORDTS SYNDROME

Table XV presents 15 cases compatible with the Heerfordt type syndrome 11 women and four men when all the patients with at least two of the following organs affected were referred to this category uvea the parotid gland the lacrimal gland and the facial nerve Three cases corresponded to the classical clinical picture while the others were incomplete All presented not only the manifestations listed in the table but also other both thoracic and extrathoracic signs of sarcoidosis Four had symptoms of involvement of other lower cerebral nerves or peripheral neuropathy Parotitis facial palsy and lacrimal gland enlargement *were the initial* and transient manifestations Uveitis was not diagnosed until weeks or even months later

In three cases reduced *lacrimal secretion and facial palsy were seen* in one and the same patient The palsy disappeared in a matter of weeks whereas the reduction in lacrimal secretion was a permanent change

TABLE XIII

The non ophthalmic manifestations of sarcoidosis in uveitis

Uveitis	Total	Intra thoracic	FN	Skin	Joints	Periph lymph	Parotid	Facial palsy	Other neurol	Bones	Hyper calc	Total
Acute	9	9	1	3	[illegible]		1	1	[illegible]	0	0	[illegible]1
Chronic	13	1	3	4	4	[illegible]		3	3	0	4	37
Total	2	1	4	7	6	4	3	4	5	0	4	58

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Acute	9	1	4	1	0	0	6
Chronic	13	4	6	1	1	4	1[illegible]
Total	[illegible]	5	10	2	1	4	[illegible]

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25—34	3	(1)	2		5/113	4
35—44	4	(2)	3		7/74	9
45—54	1		3		4/49	8
55—64	1		2		3/16	19
≥ 65	0		0		0/3	0
Total	9		13			

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Chronic	13	12	3	4	4	2	–	3	3	0	4	37
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Chronic	13	4	6	1	1	4	16
Total	--	5	10	2	1	4	22

TABLE XV

Heerfordt's syndrome and its manifestations

Only positive findings have been entered

Patients			Manifestations					
Age of onset Sex Male m Female f			Uveitis	Enlarged parotid	Facial palsy	Enlarged lacrimal gland	Reduced lacrimal secretion	Two or more other manifestations
1	40	m	+	+		+	+	+
2	48	f	+	+			+	+
3	40	f	+	+	+	+	+	+
4	19	m	+		+		+	+
5	42	f	+		+		+	+
6	52	f	+		+			+
7	64	f	+				+	+
8	59	f	+				+	+
9	27	m	+				+	+
10	23	m	+				+	+
11	32	f	+				+	+
12	49	f		+			+	+
13	43	f		+	+	+		+
14	38	f		+		+	+	+
15	43	f		+			+	+

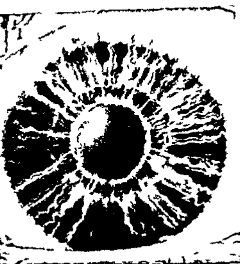
Eleven of the 22 cases of uveitis seven of the 13 cases of parotitis five of the nine cases of facial palsy, and 13 of the 32 cases of keratoconjunctivitis sicca belonged to the group referred to as Heerfordt's syndrome Lacrimal gland affection was the most common finding of the syndrome

Typical case reports are presented on pages 81—82

c ANTERIOR UVEITIS

In only one of 22 cases of uveitis was the affection limited to the anterior segment of the eye (Case 12 Table X) In all other cases at least the vitreous was affected and in 15 cases the fundus also In five patients *(Cases 3 4 6 10 and 17 Table X)* granulomas (nodules) of varying size were observed on the iris during the follow up period whereas in 17 patients no such nodules could be seen on the iris

The signs of anterior inflammation in the non nodular uveitis were slight the aqueous flare was weak and number of cells in the anterior



A



B

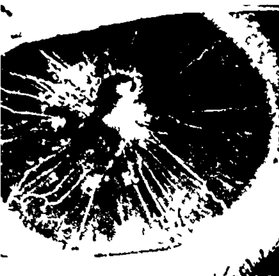
Fig Case 5 Table X Fluorescein iris angiogram Left eye in non nodular iritis A Arteriovenous phase B Late venous phase Slight leakage from the capillaries of the pupillary margin

chamber was low Fatty precipitates on the cornea were seen in only four non nodular cases

The fluorescein angiography of the iris in non nodular uveitis showed slight leakage of fluorescein from the capillaries of the pupillary margin but otherwise the angiographic finding did not differ from normal (Figs 2A 2B)

In four of the five cases of uveitis in which granulomas were seen on the iris the course of the disease was chronic with several phases of exacerbation during on average four years of follow up In one case the uveitis healed in five months and did not recur during the 3 1/2 years of follow up this case was therefore classified as acute

In some cases there were only isolated granulomas while in others at the first onset or exacerbation of uveitis the iris tissue was filled with nodules The granulomas varied in size the largest equalled in size the radius of the iris and the smallest, which were mostly located around the pupillary part of the iris were only the size of large precipitates The largest granulomas were greyish yellow or greyish red in colour with a surface covered by a network of dilated vessels and neovasculature In some cases nodules could faintly be discerned in the deeper parts of the iris and they could best be visualised by illuminating them indirectly The nodules in the pupillary area were often translucent and grey in





A B

Fig 3 Case 3 Table X Fluorescein iris angiogram Left eye A Arteriovenous phase Localised areas of irregular superficial neovascularisation (arrows) in the pupillary and the ciliary part of the iris Pupil irregular due to posterior synechiae B Late venous phase Intense leakage in the areas of neovascularisation Mild staining and leakage of the radial veins (arrows) all over the iris

colour Neovasculature was frequently seen on the surface of the nodes along the pupillary margin

Anterior reaction in nodular iritis was more pronounced than in non-nodular the aqueous flare was stronger and fatty precipitates were seen in every case The vitreous reaction also was more pronounced in these eyes

The nodules seen with the biomicroscope in fluorescein iris angiography appeared as hyperfluorescent patches (Figs 4A 7A, 9A 11A) which in the angiogram always exceeded the number of nodules revealed by biomicroscopy alone Every angiogram revealed nodules in the pupillary part of the iris In two patients the nodules were arranged like a string of pearls around the pupillary aperture (Figs 4A 4B 11A)

The small fresh granulomas themselves did not stain with fluorescein in the early phases of the angiogram It seems that their hyperfluorescence (Figs 4A 4B) was due to dilatation of the vessels both capillaries and the larger radial vessels running across the granulomatous areas and to their pronounced leakage In the areas of long-standing nodules on the iris especially among the major nodules there was superficial irregular and tortuous neovascularisation which markedly leaked fluorescein (Figs 3A 3B 4A 4B 7A 11A) In the active stage of the disease some leakage was observed from all the vessels of the iris (Figs 3B 4B) In three cases



A



B

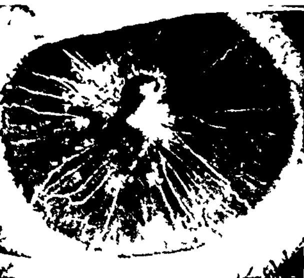


C



C

Fig 4 Case 3 Table X Fluorescein iris angiogram Left eye A New areas of superficial neovascularisation (black arrows) and small areas of deep staining (white arrows) in the iris tissue B Dilatation and leakage of the radial vessels at the site of the deep nodules (arrows) C Infrared transillumination photograph of the same phase Stereo pair The pupillary area is full of round trans lucent lesions Intact sphincter is left only in the upper temporal segment. One ciliary area nodule can be seen as a weak shadow (arrows)





A B

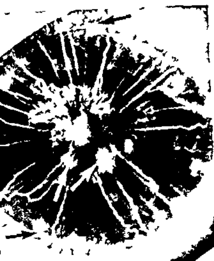
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A



B



C



C

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A B

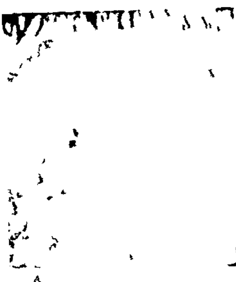
Fig 5 Case 4 Table X Fluorescein iris angiogram Left eye at the time of the second exacerbation A Tortuous dilated leaking vessels particularly in the upper temporal quadrant (arrow) corresponding to the area of a large granuloma occupying the whole iris from the pupil to the periphery Visualisation of the vessels was masked by the heavy pigmentiation of the iris B Massive fluorescence of the aqueous was seen for several hours





A B

Fig 6 Case 4 Table X Infrared transillumination photographs of (A) the right and (B) the left iris 18 months after the phase shown in Fig 5 Aphakia in the right phthisis in the left eye The radial and circular folds of a normal iris have almost completely disappeared and the sphincter areas have been destroyed

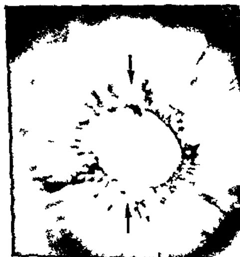




A B

Fig 7 Case *6* Table X Fluorescein iris angiogram Left eye at the time of *diagnosis* A Two large and one smaller area of neovascularisation with details beautifully visible in the early arteriovenous *phase* A distinct leakage already in this phase B Infrared transillumination photograph of the same *phase reveals* the granulomas and the lesions in the pupillary area at posterior synechiae

Fig 8 Case *6* Table X Infrared tran illumination photograph of the same eye as in Fig 7 three months later reveals how well the granulomas ha e resolved There are *only* two pupillary area defects left (arrows) which became permanent and corre spond to the defect in *pigment* epi thelium at the posterior synechiae







A B

Fig 5 Case 4 Table X Fluorescein iris angiogram Left eye at the time of the second exacerbation A Tortuous dilated leaking vessels particularly in the upper temporal quadrant (arrow) corresponding to the area of a large granuloma occupying the whole iris from the pupil to the periphery Visualisation of the vessels was masked by the heavy pigmentiation of the iris B Massive fluorescence of the aqueous was seen for several hours



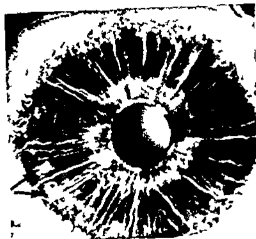


A B

Fig 6 Case 4 Table X Infrared transillumination photographs of (A) the right and (B) the left iris 18 months after the phase shown in Fig 5 Aphakia in the right phthisis in the left eye The radial and circular folds of a normal iris have almost completely disappeared and the sphincter areas have been destroyed



A



B

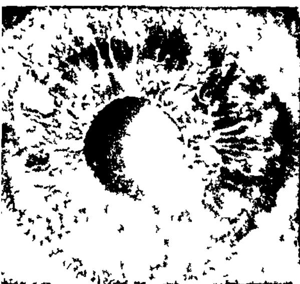


C



D

Fig 10 Case 10 Table X Bilateral fluorescein angiogram 5 months after the phase shown in Fig 9 A Left iris Abnormal superficial tortuous vessels still present Considerably less leakage than earlier B Right iris The right iris also is affected disclosing similar although milder sequelae (arrows) C and D Corresponding infrared transillumination photographs on the left (C) and the right (D) iris A defect in the pigment epithelium of the peripupillary area of the left eye (arrow) Slightly increased translucence in the peripupillary area of both eyes




A B

Fig 9 Case 10 Table X Fluorescein iris angiogram Left eye on the patient's admission for treatment A In the early arterial phase fluorescein appears in several superficial neovascular areas which within a few seconds cover most of the iris All vessels leak fluorescein B Ten minutes after A Fluorescence of the aqueous blurs the details

recurrent exacerbations of the inflammation showed repeatedly new granulomatous areas as well as activation of the earlier areas (Figs 3—4 11B—12)

After the active inflammation had subsided the leakage usually decreased or stopped although the pathological vasculature remained on the iris surface (Figs 10A 10B) In two cases however the leakage persisted even in the cicatricial areas (Figs 4B 5B) In one case (Case 4 Table X) the normal vasculature of the iris could not be seen partly because of the high pigmentation of the iris and the whole iris was covered with a neovascular network which leaked fluorescein The fluorescence was visible for hours after the injection (Figs 5A 5B)

Bilateral fluorescein iris angiography revealed that the inflammation was bilateral in four of the five cases while in each case one eye was more heavily affected than the other (Figs 10 11) In the initial phase leaking nodules were only seen in the more heavily affected eye but on exacerbation they occurred in the less affected eye as well (Figs 11 A 11 B 12 A)

Infrared transillumination of the iris was especially useful in revealing the granulomas of the pupillary region and defects of the pigment epithelium (Figs 4 C 10 C 11 C 11 D 12 B) In all the 16 cases of uveitis in which the infrared transillumination was carried out it was found that





A B

Fig 1 Case 17 Table X Six months after the phase shown in Fig 11 during systemic corticosteroid treatment A Right iris A fresh active focus at the pupillary margin (arrow 1) with a leakage in its area in the early arterial phase The second light coloured patch (arrow 2) is a reflection from the camera B The corresponding area is visible in the infrared transillumination photograph (arrow)

the pigment epithelium of the pupillary region had suffered Some granulomas of the ciliary part of the iris were also visualised (Figs 4 C 7 B) Not all the nodules seen by fluorescein iris angiography or even by biomicroscopy were revealed by the transillumination pictures (Figs 4 A 4 B 4 C) In three patients the infrared transillumination showed that the iris structure was well preserved in two of them despite a protracted course of the illness (Figs 8 10 C 10 D) whereas in two patients the disease led to a considerable destruction of the structure of both irises (Figs 6 A 6 B)

d POSTERIOR UVEITIS

Signs of posterior uveitis were observed in 21 of the 22 patients (Table X) These 21 patients showed vitreous cells and opacities in the active stage of the disease The reaction was most pronounced in the lower part of the vitreous Nine patients had so-called snowball opacities both close to the retina and towards the central part of the vitreous They were small in size apart from one case in which some were equal in diameter to the optic disc The intensity of the vitreous reaction correlated also with that of the anterior reaction All the four cases in which the vitreous in the active stage was most opaque also showed e g iris nodules

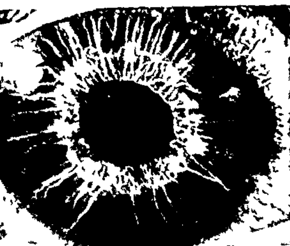








Fig 11 Ca e 17 Table X Bilateral fluorescein iris angiogram A second exacerbation during systemic corticosteroid treatment two years after the onset A Left iris Early filling of the superficial neovasculature in the area of active granuloma with considerable leakage (arrow 1) Peripupillary capillaries are dilated with areas of presumed deep granulomatosis and superficial neovascularisation (arrows 2) B Right iris Capillary congestion and leakage in the peripupillary area C and D Infrared transillumination photograph of the same phase in the left (C) and right (D) iris The meshlike structure of the pupillary areas is visualised The left pupil is larger than the right





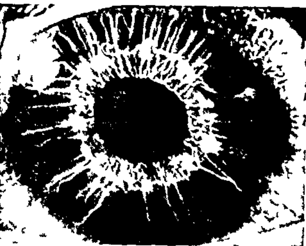
A B

Fig 12 Case 17 Table X Six months after the phase shown in Fig 11 during systemic corticosteroid treatment A Right iris A fresh active focus at the pupillary margin (arrow 1) with a leakage in its area in the early arterial phase The second light coloured patch (arrow 2) is a reflection from the camera B The corresponding area is visible in the infrared transillumination photograph (arrow)

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A



B



C



D

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Fig 15 Case 17 Table X. Typical scars left by taches de bougie exudates

Multiple chorioretinitis foci were found in the fundus of seven patients In one at the time of an activation of anterior uveitis extensive scars were found at the posterior pole (Case 13 Table X) In all the others isolated foci were located anteriorly to the equator of the fundus In the active stage the changes were not studied with fluorescein angiography since visualisation was impaired by the vitreous reaction Scars left by inflammation are seen in Figs 13 and 14 A 14 B Three patients showed chorioretinal scars but active uveitis was not observed during the years covered by the present study

2 RETINAL AND OPTIC DISC CHANGES

Local perivenous exudates i e so called taches de bougie formations were identified in 10 patients around peripheral venules The exudates occasionally assumed a string of pearls position and concealed the details of the venule running inside Five patients additionally showed extensive periphlebitis and four of these also had taches de bougie formations In the active stage the vasculitic changes occasioned a leakage of the dye in retinal fluorescein angiography In two patients (Cases 11 and 16 Table X) with symptoms of chronicised sarcoidosis also elsewhere in the system vasculitic areas of active appearance and taches de bougie formations were still seen after 3 ½ and 5 years of follow up On healing the taches de-bougie formations left typical white chorioretinal scars The lesion



Fig 13 Chorioretinal scars in a patient with sarcoidosis. No active uveitis was diagnosed



A



B

Fig 14 Case C Table X Fluorescein angiogram of the fundus. Left eye. A Arteriovenous phase. Hyperfluorescence due to the window effect of the atrophic chorioretinal scars (arrows 1) along a peripheral retinal vein at the border of the vascularised retina. Hypofluorescent network due to pigment proliferation (arrow 2). B Late picture. Persistent hyperfluorescence (partly autofluorescence) of the atrophic areas is crossed by choroidal vessels. No signs of activity in the lesions except mild localised leakage from the veins (arrows 3) corresponding to taches de bougie exudates



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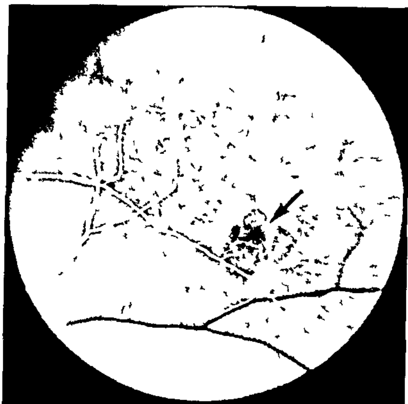
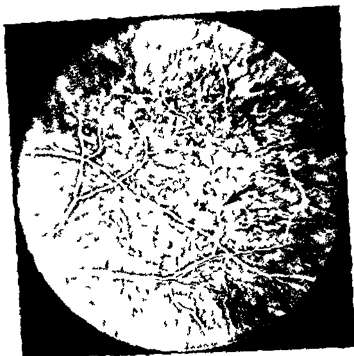


Fig 16 Case 1 Table X Fluorescein angiogram of the retina Left eye A Early arterial phase A small dark patch obscures choroidal fluorescence under a retinal vein (arrow) B Arteriovenous phase Venous branches at the site of the retinal lesion are irregular and dilated partly buried in the exudate (arrow) Choroidal structures probably normal C Late picture Intense patchy hyperfluorescence of the lesion (arrow) D Retinal photograph of the same area one month later New lesions along the course of the previously affected vein (arrows 1) and under the main vein (arrow 2)

extended through the pigment epithelium to the inner choroid layers and was also situated underneath a vessel (Fig 15)

Two patients had a transient macular oedema in the active stage of uveitis and one developed cystoid macular oedema as a result of inflammation of over 10 years duration (Case 1 Table X) The only case of retinal detachment in the series was ascribed to peripheral vasculitis and the accompanying exudation and traction (Case 16 Table X)

Retinal granulomatosis was observed in two patients In one of them (Case 1 Table X) granulomas appeared in the retina 10 years after the onset of chronic uveitis A sarcoid lung change had been observed a year before the retinal lesion and the lung lesion was resolved in six months (see pages 82—83 for the case report)


B


C



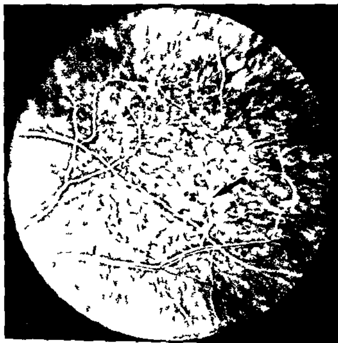
A

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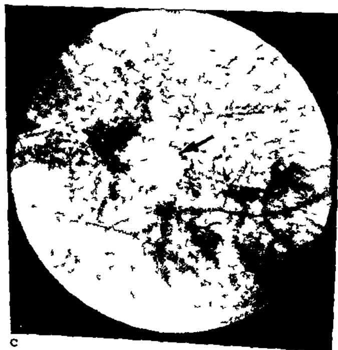
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B



C



D

Fluorescein angiography revealed a lesion associated with the retinal venules There was initial hypo- and late hyperfluorescence of the area (Figs 16 A, 16 B 16 C) After a month the granulomatosis could be seen to have expanded and moved over to a bifurcation of the venule nearby (Fig 16 D)

Granulomatosis of the retina and optic disc was documented in another patient (Case 6 Table X) in connection with the fourth attack of nodular iritis 3 1/2 years after the manifestation of the disease (see page 83 for the case report)

Fluorescein angiography of the retina revealed that the granulomas of both the retina and the optic disc were sharply defined and distinctly elevated either pushing the retinal vessels aside or hiding them from view The fresh granuloma did not fluoresce in angiography whereas intense late fluorescence was observed in the older ones as a result of secondary vascular changes (Figs 17 A 17 B 17 C)

3 THERAPY COMPLICATIONS AND VISUAL PROGNOSIS IN UVEITIS

Therapy Uveitis was treated topically with 0 1 % dexamethasone sodium phosphate and 14 patients were given oral prednisolone as well Dexamethasone was usually first instilled hourly during the daytime A maintenance dose of 2—3 drops/day was continued for weeks and sometimes months The initial do e of oral prednisolone was 30—50 mg every second morning The dose was gradually reduced over 2—3 weeks to a maintenance dose of 5—10 mg which was often continued for months

The therapy had a favourable initial effect on all the cases The inflammation subsided in the course of weeks or months The granulomas diminished gradually and finally it became impossible to discern them with a biomicroscope In some cases fresh granulomas reacted very quickly to topical treatment dexamethasone could make the freshly developing iris nodules fade away in a few days

However after the treatment was discontinued many a chronic uveitis flared up again In some cases the exacerbation took place during systemic prednisolone therapy after the dose had been reduced to maintenance level In nine cases corticosteroid therapy failed to lead to final recovery and at the end of the present study period the uveitis was still active requiring treatment

Complications produced by uveitis are listed in Table XVI

In seven patients the course of the disease was complicated by glaucoma In five the sarcoidosis manife ted itself with hypertensive uveitis After the inflammation had sub ided the pressure fell to the normal level in three but remained at a level requiring surgery in two One of these patients underwent iridectomy of one eye and the other trabeculectomy of one eye Two patients developed glaucoma as a result of the cortico-

TABLE XVI

Complications of uveitis

Complication	N (eyes)
Glaucoma	13
Cataract	9
Cystoid macular oedema	1
Retinal detachment	1
Phthisis	1
Total	25



D

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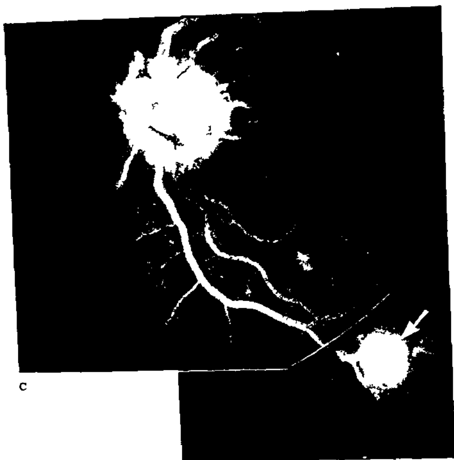
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A

B



C

Fig 17 Case 6 Table X Fluorescein angiogram of the retina Left eye A Arteriovenous phase The optic-disc granulomas are covered by some dilated leaking vessels and surrounded by dilated capillaries (arrows 1) The temporal margin of the optic disc shows a hypofluorescent superficial patch a fresh granuloma (white arrows) At the bottom of the picture a retinal granuloma (arrow) B Late venous phase Intense fluorescence from the dilated capillaries around the granulomas C Late picture Intense leakage in the area of the lesions The retinal granuloma covers the retinal vein (white arrow)

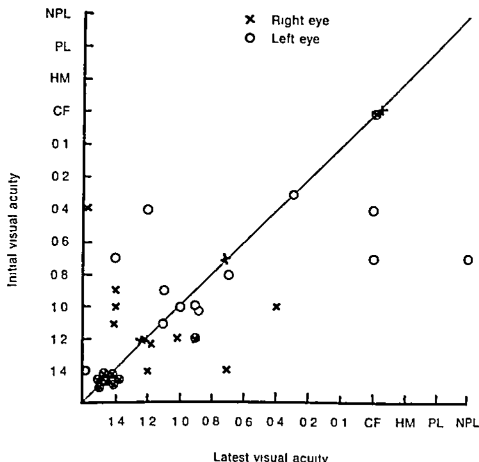


Fig 18 Graph showing initial versus latest visual acuity of 22 patients (44 eyes) with uveitis Diagonal straight line = line of no change CF = counting fingers HM = hand movement PL = perception of light NPL = no perception of light

steroid treatment and the pressure fell as soon as the treatment could be abandoned

In three patients the glaucoma caused a monocular relative para central visual field defect

Six patients developed cataract in a total of nine eyes One patient had to undergo operation for bilateral cataract while uveitis was active because of imminent capsular rupture (Case 4 Table X) One lens of one patient became completely opaque Four patients developed a slight posterior capsule cataract during the course of the long standing uveitis and corticosteroid therapy

One patient developed permanent cystoid macular oedema following a chronic uveitis of several years duration (Case 1 Table X) Another patient developed detachment of the retina following rupture caused by vasculitis and traction (Case 16 Table X)

One eye rapidly became phthisic as a result of a violent treatment-resistant exudative fibrotic process (Case 4 Table X) (see page 83 for the case report)

Prognosis The effect of uveitis on visual acuity is shown in Fig 18 The visual acuity of 12 eyes of eight patients deteriorated during the follow up period Pronounced deterioration was found bilaterally in one of them with complete loss of sight in one eye (Case 4 Table X) and unilaterally in three In 24 eyes visual acuity remained unchanged and in 8 eyes it improved In one patient (Case 13 Table X) vision had deteriorated in one eye to counting fingers and in the other ad 0 3 by the time the patient came to be included in the present series sarcoidosis manifesting itself with lung changes and anterior uveitis A sarcoid etiology of fundus scars could not be ruled out

4 SARCOIDOSIS OF THE CONJUNCTIVAE

Episcleritis In the initial phase of sarcoidosis five patients presented a clinical picture of episcleritis dilatation of the vessels of bulbar conjunctiva and episclera without any sign of uveitis The symptoms consisted of reddening of the eyes and slight photophobia In four of the five the episcleritis manifestations coincided with the appearance of erythema nodosum nodes (Table VIII) and subsided within a few months as the nodes disappeared In no case did conjunctival biopsy reveal granulomas compatible with sarcoidosis

Clinical picture and symptoms of conjunctival sarcoidosis Sarcoid conjunctival nodules were hardly discernible by the naked eye In the course of the study increasing knowledge made them ever more readily identifiable by biomicroscopy and typical features were noted Most frequently the sarcoid nodules were situated on the conjunctiva of the lower lid tarsus or the lower fornix mostly in the temporal region They were often isolated and in 10 of the 35 cases unilateral but occasionally numerous On four occasions nodules were seen in the area of the caruncle and twice on the bulbar conjunctiva close to the fornix The nodules were yellowish in colour and of varying size Sarcoidosis of conjunctivae seldom produced symptoms (Table VI) Four patients however showed reddening and oedema of the conjunctiva which in one patient had persisted for over a year In one patient large vegetations developed on lower lid conjunctivae and on the lower fornix The discomfort they caused prompted him to seek treatment At the same time the cutaneous scars of this patient grew larger and II sarcoid changes appeared in the lungs



Fig 19 Conjunctival sarcoidosis Two subepithelial epithelioid cell granulomas (arrows) surrounded by lymphoplasmocytic infiltration H—E × 50

Histological picture Conjunctival biopsies were taken from 218 patients Epithelioid cell granulomas under intact epithelium were interpreted as having been produced by sarcoidosis They were surrounded by a more or less complete lymphoplasmocytic infiltration Leucocytes were seldom seen whereas isolated giant cells were frequent



Fig 20 Fibrinoid necrosis (arrow) visible in the middle of the epithelioid cell granuloma H—E × 128

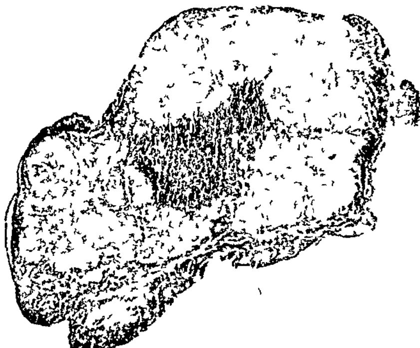


Fig 21 A Conjunctival sarcoidosis A section tightly packed with granulomas H—E x 50

No asteroid or Schaumann s bodies were seen in any of the cases In five cases the granuloma was composed of only a small bunch of epithelioid cells not always even visible in contiguous sections In 16 patients the isolated granulomas were sizable (Figs 19 20) In another 16 patients they were numerous and in eight cases the tissue specimen was so packed with granulomas that no tissue of intact appearance could be seen (Figs 21 A 21 B) In two specimens there was a fibrinoid necrosis in the middle of isolated granulomas (Fig 20)

Biomicroscopy of the conjunctival nodule had aroused suspicions of sarcoidosis in 66 cases These suspicions were confirmed by histological examination in 27 i e 40 9 % of the cases Conjunctival biopsy revealed unsuspected sarcoidosis in 10 i e 6 6 % of the 152 subjects in whom nodules either were not seen at all or although seen were not thought to be sarcoid (Table XVII) The difference is highly significant ($p < 0\ 001$)

In 69 patients the upper lid conjunctiva was also examined Nodules were found in 17 but sarcoidosis was histologically confirmed in only one In four of these 69 patients the lower lid nodule however produced a histological sarcoid finding



Fig 21 B Part of Fig 21-A × 128 The granuloma presents a uniform histological picture of weakly staining epithelioid cells Multinuclear cells are visible here and there (arrows) H—E staining

Conjunctival granulomas found in the biopsies were relatively equally numerous irrespective of the interval from the onset of the disease (3 months to 6 years or over)

The histology of the conjunctival biopsy of the other patients of the series (181 out of the 218) was the following lympho- and plasmocytes either isolated or assembled in diffuse infiltrates in 72 cases In 77 specimens they were follicularly organised and in 32 cases there were follicles with a germinal centre

The conjunctival tissue biopsies of the control series of 40 subjects contained no epithelioid cell granulomas Twenty-five specimens showed a diffuse lymphocytic infiltration and another 15 showed follicularly organised mononuclear inflammatory cells six of them with a germinal centre

TABLE XVII

Histological findings in conjunctival nodules suspected as sarcoid

Suspicion of conjunctival granuloma	Total	Histological finding compatible with sarcoidosis		Histological finding incompatible with sarcoidosis	
	N	N	%	N	%
Yes	66	27	40.9	39	59.1
No	152	10	6.6	142	93.4
Total	218	37	17.0	181	83.0

Sarcoidosis of conjunctivae and other ophthalmic manifestations (Table XVIII) The table shows that every fourth patient with uveitis almost one-third of those with keratoconjunctivitis sicca two-fifths of the patients with band keratopathy and two thirds of those whose lacrimal gland was pathologically enlarged also had sarcoidosis of the conjunctivae All these ratios exceed the relative proportion (17 %) of sarcoidosis of conjunctivae in the total series

Sarcoidosis of conjunctivae and extraophthalmic manifestations (Fig 2.) Every patient with sarcoidosis of conjunctivae also had pulmonary manifestations In connection with I° change in chest radiograph 9.9 % of the conjunctival biopsies showed epithelioid cell granulomas *In connection* with II° and III lung finding the sarcoidosis of conjunctivae was diagnosed more frequently in 23.8 % and 42.9 % of those examined *respectively* When fibrotic changes were seen in the lungs sarcoidosis of conjunctivae was a highly significantly ($p < 0.001$) more frequent finding than when the disease was manifested with I° changes Conjunctival

TABLE XVIII

Conjunctival sarcoidosis related to other ophthalmic sarcoid manifestations

Ophthalmic manifestation	Number of conjunctival biopsies	Histological finding compatible with sarcoidosis	
	N	N	%
Reduced lacrimal secretion	30	9	30
Uveitis	0	5	25
Band keratopathy	10	4	40
Enlarged lacrimal gland	6	4	67
Dacryostenosis	5	1	20

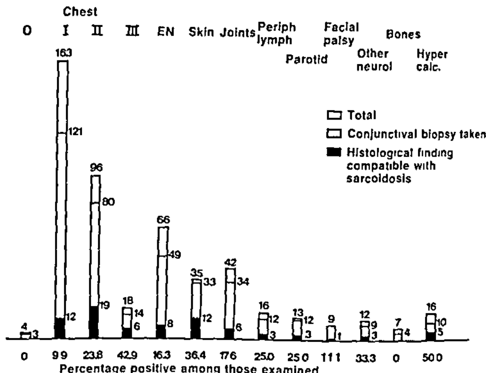


Fig 22 Histologically confirmed conjunctival sarcoidosis in association with other sarcoid manifestations

granulomas were found in 12 % of the cases even after the lung lesion had regressed but they occurred in 47 % that is to say significantly ($p < 0.01$) more often when fibrosis could be seen to be developing in the lungs (Table XIX)

TABLE XIX

Trend of development of the chest radiograph at the time of the conjunctival biopsy in relation to the histological finding

Finding in chest radiograph compared with the preceding	No of conjunctival biopsies	Histological finding compatible with sarcoidosis N	%	incompatible N	%
Disappeared	69	8	12	61	88
Regressing without fibrosis	68	12	18	56	82
Unchanged	45	6	13	39	87
Progressing	19	4	21	15	79
Regressing or progressing with fibrosis	15	7	47	8	53

TABLE XX

Activity of sarcoidosis at the time of the conjunctival biopsy in relation to the histological finding

Activity	No of conjunctival biopsies	Histological finding compatible with sarcoidosis N	%	incompatible with sarcoidosis N	%
Active	60	21	35 0	39	65 0
Inactive	158	16	10 1	142	89 9
Total	218	37	17 0	181	83 0

All the other extraophthalmic manifestations of sarcoidosis discussed in the present study were also found in patients with sarcoidosis of the conjunctivae The simultaneous appearance of cutaneous lesions and conjunctival changes in the same patient (12 out of 33) was common Conjunctival granulomas occurred highly significantly more often ($p <$ 0 001) in the active than the inactive stage of sarcoidosis (35 % and 10 % respectively Table XX) in which the patients were symptom free and/or their lesions had regressed or shown no change for at least one year

5 SARCOIDOSIS OF LACRIMAL APPARATUS

a LACRIMAL GLAND

Symptoms (Table VI) Twelve patients were experiencing discomfort due to dryness of the eyes — a feeling of a foreign body in the eye — when they first came for an ophthalmological examination and one developed mild symptoms of dryness during a follow up period of 3 1/2 years One had to take permanent recourse to artificial tears Six patients had an enlarged lacrimal gland that in two of them was visible and in four palpable In two the enlargement of the gland was accompanied by transient cessation of lacrimal secretion

Objective finding The lacrimal secretion was examined by Schirmer's test When a lessening of secretion was suspected the test was repeated three times The results of Schirmer's test for 254 patients are given in Table XXI In 43 eyes the Schirmer result was ≤ 7 mm In 70 eyes the test result was within the borderline range of 8—15 mm average 11 5 mm The Rose Bengal test was carried out on 36 patients No staining whatever was observed in 9 Staining reactions of different

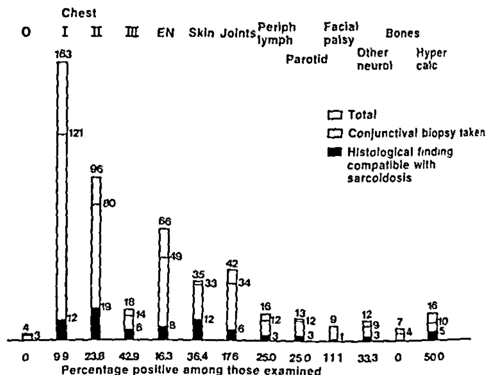


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Fig 23 Sarcoidosis in the lacrimal sac Four epithelioid cell granulomas of old appearance with fibrotic changes in the surroundings H—E x 32

lacrimal secretion (Table VIII) Of the 15 patients grouped under Heerfordt s syndrome 13 showed a reduced lacrimal secretion which was also found in 10 of the 21 patients presenting nervous system symptoms

b LACRIMAL PASSAGES

Five female patients had epiphora due to dacryostenosis Three of them had moreover suffered for years from nasal obstructive symptoms All five had chronic generalised sarcoidosis Dacryocystorhinostomy was carried out on three In one the stoma remained patent while in the other two even a re-operation failed to lead to the desired result For two the removal of the lacrimal sac was chosen as the primary method

TABLE XXI

The result of Schirmer's test in 254 patients with sarcoidosis

Right/left eye	Moistening of the test strip in 5 min							
	≤ 7 mm		8—15 mm		≥ 16 mm		Total	
	N	%	N	%	N	%	N	%
Right eye	19	7 5	38	15 0	197	77 5	254	100 0
Left eye	24	9 4	32	12 6	198	78 0	254	100 0
Total	43	8 5	70	13 8	395	77 7	508	100 0

degrees were recorded on the conjunctivae and cornea of one eye in five and both eyes in 22 patients

Lacrimal secretion was classified as pathologically reduced if the Schirmer value was ≤ 7 mm or if, with a Schirmer value of 8—15 mm the Rose-Bengal test was positive However, if the lacrimal film was smooth if signs of epithelial degeneration were absent, and if no filaments were visible on the corneal or the conjunctival surface the lacrimal secretion was assessed as adequate even if the Schirmer value was within the borderline range According to this assessment the lacrimal secretion of a total of 32 patients was reduced

The ages of the patients with reduced lacrimal secretion ranged from 19 to 64 mean 38 5 years The mean age of the symptom-free patients with keratoconjunctivitis sicca (35 1 years) was considerably lower than that of the patients with symptoms (44 2 years)

The lacrimal gland function of 29 patients with keratoconjunctivitis sicca was observed for periods varying from two to five years In 22 Schirmer's test after the observation period was still below 7 mm In 18 of these patients, signs of chronicised sarcoidosis could also be observed elsewhere in the organism In four patients other manifestations of sarcoidosis were no longer found The lacrimal secretion of seven patients was restored in 1—2 years In three of them the sarcoidosis elsewhere in the organism became chronic whereas in four all the other signs of the disease disappeared as well

Reduced lacrimal secretion and other ophthalmic manifestations Reduced lacrimal secretion was common in patients with other ophthalmic manifestations of sarcoidosis It was recorded in nearly a half of those who had uveitis or band keratopathy and in one third of those with sarcoidosis of conjunctivae

Reduced lacrimal secretion and other manifestations of sarcoidosis Sarcoid skin lesions were seen in 15 of the 32 patients with reduced



Fig 23 Sarcoidosis in the lacrimal sac Four epithelioid cell granulomas of old appearance with fibrotic changes in the surroundings H—E x 3?

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6 BAND KERATOPATHY AND HYPERCALCAEMIA

In 11 patients the corneal change was classified as band keratopathy In connection with band formation, white crystals of varying number and size were always seen even in the limbal conjunctival areas, in the region of the palpebral fissure

Ophthalmological examination included the study of serum calcium in 222 patients An elevated Ca level ($>$ 2 6 mM/l) was recorded in 16, in 11 of them the hypercalcaemia was transient with normal control values, and mild ($<$ 2 9 mM/l) In five (2 %) the hypercalcaemia persisted for months with values ad 3 5 mM/l measured in one patient These five patients had an extensive generalised sarcoidosis and renal insufficiency Two showed a condition similar to episcleritis, and photophobia *when the calcium levels were at their highest*

Table XXII shows the interrelationship between band keratopathy and the serum calcium level In seven of the 11, i e 64 % of the patients with *band keratopathy, the level exceeded 2 6 mM/l* In only nine (4 %) of the 211 patients with sarcoidosis in whom no band keratopathy was observed, the serum calcium levels were within the range of 2 6—2 89 mM/l The difference is highly *significant ($p < 0\ 001$) The same*

TABLE XXII

Band keratopathy in relation to serum calcium level

Serum calcium (mM/l)	Band keratopathy Yes N	No N	Total N
< 2 0	0	0	0
2 0—	0	13	13
2 2—	1	78	79
2 4—	3	111	114
2 6—	4	9	13
2 9—	2	0	2
3 2—	0	0	0
≧ 3 5—	1	0	1
Total	11	211	222

causal connection is emphasised by the acceleration of crystal formation observed in three patients while the calcium levels were at their highest and the decrease (in one disappearance) of the crystals as the calcium level returned to normal during corticosteroid therapy

Band keratopathy was found in four patients with uveitis but all these also showed hypercalcaemia In one the chronic uveitis may also have caused the band keratopathy In the other three the band formation did not follow the course of the uveitis Five patients with keratoconjunctivitis sicca had band keratopathy and three of these also hypercalcaemia.

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≥ 3.5—	1	0	1
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sarcoidosis was the lacrimal secretion found to be reduced (James et al 1964)

In this study without conjunctival biopsies and examination of the lacrimal gland function 69 of 121 manifestations i e 57 % would have escaped detection and the total of patients with ophthalmic changes would have been 43 or 15 3 % of the total series It is interesting to note that the percentage is exactly that quoted by James et al (1976b) on their international series while analysing the ophthalmic changes of 3676 patients with sarcoidosis but without devoting any appreciable attention to the conjunctival and lacrimal gland changes In their retrospective work the frequency of ophthalmic changes in different major cities of the world ranged from 0 4 % in Naples to 32 % in Tokyo Geographical differences in the frequency are possible However the assumption can not be excluded that the large differences may be due to differences in the methods of examination

The rate of uveitis in the present study 22 of 281 cases i.e 7 8 % is lower than that quoted in many earlier reports (Longcope & Freiman 1952 Wegner 1957 Crick et al 1961 James et al 1964) However the figure is of the same magnitude as in the Scandinavian reports for which the material was collected in a way comparable to the present work (Löfgren 1953b Rudberg Roos 1962 Selroos 1969) even these authors how ever had not carried out a thorough and detailed ophthalmological exa mination.

Symptoms of the ophthalmic manifestations A characteristic of sarcoidosis is that it produces in many organs less symptoms than one would expect on the basis of the finding The low rate of symptoms of ophthalmic changes has already been pointed out earlier (Österberg 1939 Smellie & Hoyle 1960) The same observation was repeated in the present study in which only 12 patients (of whom 11 had uveitis) sought treatment because of the ophthalmic symptoms The vast majority (60 %) of the ophthalmic changes had not even been noticed by the patients themselves.

Sarcoidosis as the etiological factor in endogenous uveitis In most materials the part played by sarcoidosis as the etiological factor of endogenous uveitis is small in the Japanese (Uyama 1972) however it was the most common with 17 % of the causes of endogenous uveitis (Table XXIII) In two British studies the etiological share of sarcoidosis is very different Perkins (1968) 2 % and James et al (1976a) 7 % The latter team of investigators was particularly interested in sarcoidosis In a Danish material (Nordentoft & Møller 1970) the corresponding percentage was 13 In India the most important cause of uveitis is tuberculosis and sarcoid uveitis is unknown there (Consul et al 1972) Saari et al

V DISCUSSION

Validity of the diagnosis All the patients showed a clinico-radiological or clinical finding compatible with sarcoidosis, and a histological picture of tissue specimen compatible with sarcoidosis, and therefore the diagnosis can be considered valid in all the cases

Frequency of ophthalmic manifestations Seventy-nine patients (28 1 %) had ophthalmic manifestations at some stage of the disease The frequencies of ophthalmic changes in sarcoidosis quoted in the literature range from below 10 % to over 60 % The figures are not comparable since the materials have been selected (Longcope & Freiman 1952, Crick et al 1961) the ophthalmological examinations have not been thorough (James et al 1964), and/or the studies have been restrospective (Ricker & Clark 1949, Obenauf et al 1978) The present study was prospective and hence the highest possible rate of ophthalmic manifestations was observed The material was unselected and comprised practically all the cases diagnosed within a certain area during the years covered by the study Since, furthermore a methodical and detailed ophthalmological examination of every patient was carried out by the author there is reason to believe that the frequency of ophthalmic changes in sarcoidosis in Finland is of the magnitude reported in the present study It is of course, true that many cases of sarcoidosis may still evade detection, and therefore are not included in any material This is suggested by the annual incidence of sarcoidosis obtained in the present study, which was three times that reported earlier from the same area (Selroos 1969)

Sarcoidosis of the conjunctivae and reduced lacrimal secretion were the most frequent of the ophthalmic changes in the present study, 17 0 % and 12 6 % respectively while uveitis ranked third with 7 8 % (Table V) Sarcoidosis of the conjunctivae and reduced lacrimal secretion as manifestations of sarcoidosis seem to have been unknown to many of the authors (James et al 1964, Siltzbach 1967b Selroos 1969) As late as 1976(b) in the report by James et al on 542 patients with sarcoidosis only nine conjunctival follicles were reported and in only 2 % of 442 patients with

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disease The clinical course in four cases of granulomatous uveitis was acute This contradicts Woods (1961) assertion that all cases of granulomatous uveitis are chronic It may not be at all appropriate to divide sarcoid uveitis into acute and chronic The onset was definitely acute in uveitis associated with an intense rise in pressure In all the other cases the disease began silently with few symptoms and it could take months or even a year before the patient sought treatment Five patients with uveitis had no symptoms whatever The possibility of uveitis should always be kept in mind in the case of a patient with sarcoidosis Delay in the institution of therapy may lead to the development of irreversible complications (Crick et al 1961 James et al 1964)

For some reason sarcoid uveitis seems to be more common among women than men. This observation reported earlier (Wegner 1957 James et al 1964 Perkins 1968 Uyama 1972) was again made in the present study The bilateral character of sarcoid uveitis apparent from the present series in which 20 of the 22 cases occurred at the same time in both eyes agrees with earlier reports as well (James et al 1964 Duke—Elder & Perkins 1966)

Heerfordt s syndrome At the time Heerfordt lived and worked — his report was published in 1909 — sarcoidosis was not known as a systemic disease After uveoparotid fever was found to be a manifestation of sarcoidosis (Bruins Slot 1936) the uveoparotid syndrome as a separate entity became less important Heerfordt s syndrome was considered a sign of an extensively disseminated and active form of the disease (Longcope & Freiman 1952) Also cases in which not all manifestations making up Heerfordt s syndrome were seen viz uveitis parotitis facial palsy and/or other cerebral nerve symptoms could be referred to this syndrome (Waldenstrom 1937 Bruins Slot et al 1938 Lambert & Richards 1964) Fever was often found to be absent as part of the syndrome (Garland & Thomson 1933) Heerfordt (1909) did not investigate the functioning of the lacrimal gland in his patients but in none was the lacrimal gland visibly enlarged Crick et al (1961) paid methodical attention to the function of the lacrimal gland and found that reduced lacrimal secretion together with uveitis was the most common component among the manifestations of the uveoparotid syndrome The same observation was again made in the present work The four cases of the present series with parotid and lacrimal gland affection but no uveitis might also be called Mikulicz s syndrome (Mikulicz 1892) This syndrome that contains many clinical entities need not in sarcoidosis necessarily be distinguished from Heerfordt s syndrome for which uveo-dacryo-parotitis would be a more appropriate name In the present series Heerfordt s syndrome is represented by a group of 15 patients. Only once was the diagnosis made at *first* examination This was

TABLE XXIII

The role of sarcoidosis in the etiology of uveitis in 15 series collected from the literature

Author	Year	No of patients	Etiology clarified (%)	Sarcoidosis of all patients (%)
Bennet	1955	332	63	2
Wegner	1957	1 200	?	14
Oksala	1960	100	46	1
Woods & Abrahams	1961	432 *	86	4
Bergaust	1962	247	45	<1
Haut	1966	850	48	1
Witmer	1968	114	30	2
Perkins	1968	1 846	35	2
James et al	1969	204	55	4
Nordentoft & Møller	1970	108	29	13
Imai et al	1971	1 087	43	7
Consul et al	1972	165	70	0
Uyama	1972	264	?	17
Saari et al	1975	653	24	1
James et al	1976a	368	46	7
Total		7 970	48	5

* granulomatous uveitis

(1975) published a study of uveitis covering a period of 10 years They found nine cases of sarcoidosis among 653 patients with endogenous uveitis This amount is markedly less than was found in the present study, despite the fact that the patients came from the same specific area A partial explanation of the difference is that their series included only patients with symptomatic uveitis and that they paid no specific attention to sarcoidosis On the other hand, the vast difference between the figures illustrates the shortcomings of a retrospective study It seems evident also, that the authors who really searched for sarcoid uveitis did find it (Nordentoft & Møller 1970 Uyama 1972 James et al 1976a)

The clinical picture of sarcoid uveitis The distribution of uveitis on the basis of biomicroscopic appearance was not self-evident in the cases in which in addition to a mild anterior uveitis only a few taches-de-bougie exudates or only snowball-formed opacities in the vitreous were seen However candle-wax lesions and snowball opacities in the vitreous are known (Franceschetti & Babel 1949 Gass & Olson 1975) on the basis of their histology to be epithelioid cell and lymphocyte aggregates granulomatous changes In five cases no biomicroscopic signs of granulomatous reactions were seen and the cases had to be classified as non granulomatous which is a contradiction in terms in a granulomatous

disease The clinical course in four cases of granulomatous uveitis was acute This contradicts Woods (1961) assertion that all cases of granulomatous uveitis are chronic It may not be at all appropriate to divide sarcoid uveitis into acute and chronic. The onset was definitely acute in uveitis associated with an intense rise in pressure In all the other cases the disease began silently with few symptoms and it could take months or even a year before the patient sought treatment Five patients with uveitis had no symptoms whatever The possibility of uveitis should always be kept in mind in the case of a patient with sarcoidosis Delay in the institution of therapy may lead to the development of irreversible complications (Crick et al. 1961 James et al 1964)

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Heerfordt s syndrome At the time Heerfordt lived and worked — his report was published in 1909 — sarcoidosis was not known as a systemic disease After uveoparotid fever was found to be a manifestation of sarcoidosis (Bruins Slot 1936) the uveoparotid syndrome as a separate entity became less important Heerfordt s syndrome was considered a sign of an extensively disseminated and active form of the disease (Longcope & Freiman 1952) Also cases in which not all manifestations making up Heerfordt s syndrome were seen viz uveitis parotitis facial palsy and/or other cerebral nerve symptoms could be referred to this syndrome (Waldenstrom 1937 Bruins Slot et al 1938 Lambert & Richards 1964) Fever was often found to be absent as part of the syndrome (Garland & Thomson 1933) Heerfordt (1909) did not investigate the functioning of the lacrimal gland in his patients but in none was the lacrimal gland visibly enlarged Crick *et al* (*1961*) paid methodical attention to the function of the lacrimal gland and found that reduced lacrimal secretion together with *uveitis* was the most common component among the manifestations of the uveoparotid syndrome The same observation was *again made* in the present work The four cases of the present series with parotid and lacrimal gland affection but no uveitis might also be *called* Mikulicz s syndrome (Mikulicz 1892) This syndrome that contains many clinical entities need not in sarcoidosis necessarily be *distinguished* from Heerfordt s syndrome for which uveo-dacryo-parotitis would be a more appropriate name In the present series Heerfordt s syndrome is represented by a group of 15 patients Only once was the diagnosis made at first examination This was

due to the fact that the symptoms making up the syndrome may appear at monthly or even yearly intervals There is every reason to learn to know Heerfordt's syndrome and keep in mind the possibility of sarcoidosis already in connection with any of its individual manifestations

Nodular iritis and the relevant photographic findings Nodules of the iris are typical of ophthalmic sarcoidosis and a great deal of attention was paid to them already in the early reports (Schumacher 1909, Bruins Slot et al 1938) Nodules have been observed everywhere on the iris (Österberg 1939 Woods 1949) So-called Koeppe s nodules are often seen at the pupillary margins (Koeppe 1917, Bruntse 1958), and they occasionally produce asymmetry of the pupillary aperture and a weak reaction to light (v Bahr 1938 Lewis 1941) Iris nodules were seen in five of the 22 present cases of uveitis, a figure that compares well with those quoted by the earlier authors (Österberg 1939, Crick et al 1961) In two of the present patients, also in exacerbation, the iris nodules occurred unilat erally like a string of pearls along the pupillary margin The pupil reacted poorly in one patient s eye because of posterior synechiae, in the other s eye without posterior synechiae apparently because of epithelioid cell granulomas in the region of the sphincter muscle, although internal ophthalmoplegia cannot be ruled out (Cases 3 and 17, Table X, Figs 4 11 C, 11 D)

Fluorescein angiographic or iris infrared transillumination findings in nodular iritis have previously not been described in the literature (see pp 40—47) Iris angiography which showed that there always are more granulomas than can be seen by biomicroscopy was also able to differentiate between fresh granulomas and older ones the fresh ones hypofluoresced in the early phases of angiography but hyperfluoresced in the later phases, due to the increased permeability of the iris vessels, whereas neovascularisation caused the older granulomas to fluoresce from the early phase onwards The development of epithelioid cell granulomas, often in the pupillary area, can be due to slow circulation in the iris, especially in the dense capillary plexus of the pupillary margin (Hayreh 1978) Angiography of the iris disclosed a re-dissemination of granu lomatosis in exacerbation There were both new nodules and such as had been previously seen and were seemingly healed but had become reactivated It is probable that sarcoid granulomatosis behaves in the same way in other tissues as well Angiography of the iris also showed that granuloma leaves scars that are almost or completely indiscernible by biomicroscopy Many earlier studies by biomicroscopy alone have failed to find them (Blegvad 1938 Kindt 1940) Even granulomatous changes in the less affected iris where they could not always be seen by biomicro scopy were often brought to view by bilateral iris angiography

Infrared transillumination photography of the iris revealed the pigment epithelium defects occasioned by sarcoid uveitis Such pigment epithelium defects in the iris are rare in healthy subjects under 45 years of age (Norn 1971 Saari et al 1977) In all the present patients with uveitis even the 15 under 45 the pigment epithelium of the pupillary area had suffered some damage In nodular iritis the epithelioid cell granulomas of the pupillary part of the iris appeared as translucent round lesions or as round pigment epithelium dots left behind by the healed granulomas The infrared transillumination photography of the iris showed the twofold behaviour of sarcoid uveitis iris granulomatosis may heal completely leaving a nearly healthy looking iris behind (Fig 10 D) or it may lead to the destruction of the eye and almost none of the normal structure of the iris will be left (Figs 6 A 6 B)

Posterior uveitis retinal and optic disc changes Vitreous opacities in the early phase of the disease were observed in 21 of the 22 patients with uveitis and fundus lesions were seen in 15 which shows that sarcoid uveitis is almost always generalised a finding that agrees with the report by Crick et al (1961) Some authors (e g James et al 1964) considered the posterior changes to be rare a claim perhaps due to the fact that the fundus was not always examined all the way to the periphery The vast majority of the fundus lesions observed in the present study were situated in the periphery and without a three-mirror contact lens examination they might have evaded detection Furthermore in the active phase the visibility of the fundus was in some cases impaired by vitreous opacities which were often snowball opacities of the type described by Landers (1949) Changes due to nonspecific chorioretinitis were seen in one-third of the cases of uveitis while another three showed scars left by such changes without signs of active anterior inflammation The observations agree with the analysis by Gould & Kaufman (1961) The fluorescein angiography finding in the patient (Case 6 Table X) from the area of chorioretinitis shows that granulomatosis may extend through the choroid to the sclera (Figs 14 A 14 B)

Most common among the retinal changes were the taches-de bougie exudates seen in nearly half the cases of uveitis Scars left by the lesions showed that there was a retinochoroidal change (Fig 15) *Diffuse* peri phlebitis was seen in a quarter of the cases of uveitis Systematical fluorescein fundus angiography might have revealed even more vascular changes which according to Kobayashi (1976) almost always occur in sarcoid retinopathy

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1974, Letocha et al 1975) In the present series, retinal granulomas were found in two patients, one of whom additionally had optic disc granulomatosis (Case 1, Table X, Figs 16 A, 16 B, 16 C, 16 D, and Case 6, Table X Figs 17 A, 17 B, 17 C) Hypofluorescence in the early phase of retinal and optic disc granulomatosis, and late leakage of the adjacent vessels were analogous to the angiography finding in fresh iris nodules

Therapy complications and visual prognosis in uveitis Corticosteroid therapy, topical dexamethasone and systemic prednisolone treatment had a beneficial effect However, they did not lead to complete recovery in nine patients whose disease, at the close of the present study, was still active Recurrences were frequently seen even during the course of systemic corticosteroid therapy, an observation reported by earlier authors as well (Wegner 1957, Crick et al 1961, Uyama 1972, Kobayashi 1972)

Glaucoma was the most common complication of uveitis and corticosteroid therapy Although in only two it remained in a phase still requiring treatment, it did produce a slight visual field defect in three patients Two patients rapidly developed a mature cataract one of them in both eyes The latter had to undergo surgery for cataract in both eyes due to intumescence of the lens (Case 4 Table X, Figs 5 A, 5 B, 6 A, 6 B) Cataract operation in the active inflammatory phase was probably one of the reasons why the eye became phthisic This patient may also have had a granulomatous process in the ciliary body causing in the initial stage, a pronounced forward bulging of the iris and later contributing to the cessation of aqueous humour secretion An exudative fibrotic course of disease, resulting in blindness, has also been described by e g Wegner (1957) and Crick et al (1961)

In eight of the 22 patients uveitis had by the end of the present study period, produced permanent impairment of the vision in one or both eyes In four it had produced marked impairment of vision In the light of the present study it seems, therefore, that in sarcoid uveitis the prognosis for visual function is not so favourable as was assumed by Scadding (1967) The present author rather agrees with Kobayashi (1972) and Uyama (1972), according to whom the prognosis generally is good but complete recovery is difficult to achieve

Sarcoidosis of conjunctivae Sarcoidosis of conjunctivae was histologically diagnosed in 17 % of all the cases and in 41 % of those in which it could be suspected from the ophthalmological examination In the light of the present study sarcoidosis of conjunctivae is a manifestation considerably more frequent than uveitis Although the conjunctival nodules biomicroscopically were often typical — of different sizes isolated and yellowish in colour — they could not always be distinguished with

certainty from follicles which occur »normally» on the palpebral conjunctiva and which often are equal sized and reddish in colour

There were slight difficulties in the histological interpretation of five specimens in which the epithelioid cell aggregates were very small In all the other cases the granulomas isolated or filling the whole specimen were visible without difficulty and morphologically similar to the sarcoid epithelioid cell granulomas of any other organ They always occurred in subepithelial tissue surrounded by lymphocytes and were covered by intact epithelium No epithelioid cell granulomas were found from the conjunctiva of 40 control subjects nor have earlier authors found them from their control materials (Crick et al 1961 Bornstein et al 1962) These observations support the assumption that the conjunctival epithelioid cell granulomatosis in the present material was of sarcoid etiology The possibility of histological misinterpretation due to chalazion has been pointed out e g by Zimmerman & Maumenee (1961) As it is clinically so evident chalazion was taken for histopathological examination only once during the period covered by the present study The section contained epithelioid cell granulomas which however were deep in the middle of connective tissue and had a less homogeneous appearance than the granulomas of sarcoid origin They also contained an abundance of polymorphonuclear leucocytes which do not belong to the histological picture of sarcoidosis

Diagnostic value of conjunctival biopsy The fact that 41 % of the nodules suspected from their biomicroscopic outward appearance to be sarcoid contained epithelioid cell granulomas makes conjunctival biopsy a valuable tool in the diagnosis of sarcoidosis It is an easy and painless method free from complications and suitable for use in outpatient departments A diagnostic conjunctival biopsy is favoured by many earlier authors (Crick et al 1961 Bornstein et al 1962 Karma & Sutinen 1975 Khan et al 1977) A blind biopsy i e a specimen from a conjunctiva with no nodules is however not worth taking as was also pointed out by Crick et al (1961) Conjunctival biopsy may also be useful when other ophthalmological manifestations of sarcoidosis are suspected When pulmonary fibrosis appears to be of sarcoid etiology a conjunctival biopsy can be recommended Scadding (1967) pointed out that conjunctival biopsy unfortunately cannot be taken when it is most needed viz in the initial sarcoidosis manifesting itself intrathoracically The chronic generalised form of the disease also offers other sites of biopsy However in the present material conjunctival sarcoidosis was the only extrathoracic manifestation of sarcoidosis in 15 patients.

Sarcoidosis of lacrimal apparatus Enlargement of the lacrimal gland in the acute phase or exacerbation of the disease is uncommon It was

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noted in six patients of the present series, and relatively even less frequently in the earlier reports (Crick et al 1961, James et al 1964) However, the lacrimal gland apparently is much more often affected in sarcoidosis Schirmer's test, checked by means of the Rose Bengal test, revealed a pathologically reduced lacrimal secretion in 32 of the present patients Schirmer's test is inaccurate, and the secretion values are affected e g by the sensibility of the globe (Schirmer 1903) and the patient's age (de Rotth 1941) Crick et al (1961) found a reduced lacrimal secretion in up to 70 % of their patients This is probably too high a figure, arising from the use of the Rose-Bengal test to measure the lacrimal secretion, a test even less accurate than Schirmer's test It is characteristic of sarcoid keratoconjunctivitis sicca that it seldom gives rise to any pronounced symptoms of dryness and that the lacrimal secretion may return to normal On these points the keratoconjunctivitis sicca caused by sarcoidosis differs from Sjogren's syndrome Half the number of the present patients with keratoconjunctivitis sicca were under 40 years of age, which may be one of the reasons why there were so few symptoms (Sjogren & Bloch 1971)

Involvement of the lacrimal sac has been considered rare in sarcoidosis (Coleman et al 1972, Cook et al 1972) The nasal mucosa is probably less rarely affected (Weiss 1960, Siltzbach & Blaugrund 1963) Fisher et al (1971) thought that sarcoid tissue changes may be the cause of lacrimal stenosis The observations on the present five cases of dacryostenosis all with chronic florid sarcoidosis and three with long-standing nasal obstruction, would also suggest this Epithelioid cell granulomas were found in tissue specimens taken from the nasal mucosa of one patient and from the lacrimal sac of two others The attempts at treating the patients with dacryostenosis suggested that dacryocystorhinostomy in patients with sarcoidosis is not always a useful method

Band keratopathy and hypercalcaemia 64 % of the patients with band keratopathy had a serum calcium value exceeding the normal whereas in the total series it was elevated in only 7 % This finding supports the earlier view (Haldimann 1941 Walsh & Howard 1947 O Connor 1972) that band keratopathy in sarcoidosis is associated with the serum calcium level and occasionally reflects its fluctuations (Cogan et al 1948 Crick et al 1961 Lemp & Ralph 1977) During the period covered by the present study one patient developed an acute hypercalcaemic condition and the conjunctival and corneal change that developed in a few months contributed towards the correct diagnosis Hypercalcaemic band keratopathy may in its acute phase be accompanied by irritation symptoms of episcleritis type as was seen in two of the present patients This finding has also been reported in the literature (Crick et al 1961 Smith & Hey 1976)

Determination of serum calcium in the present study was carried out for the sole purpose of comparing the possible crystal formation on the conjunctiva and cornea with the simultaneous serum calcium level In a quarter of these patients the lung affections at the time of the comparison had radiologically resolved. Hence the calcium levels quoted do not reflect the frequency of hypercalcaemia in sarcoidosis since hypercalcaemia may appear in any phase of the disease (Scadding 1967) However it can be concluded from the results that a pathological rise in the serum calcium level cannot be very common in sarcoidosis and a similar trend is indicated by the earlier controlled prospective studies (Putkonen et al 1965 Goldstein et al 1971)

Differential diagnosis of ophthalmic sarcoid changes According to some authors many ophthalmic changes can from their outward appear ance be identified as sarcoid Such changes include iris nodules (Österberg 1939 Essen Moller 1941) vitreous opacities (Landers 1949) and taches de-bougie exudates (Franceschetti & Babel 1949) In the present study also the observed conjunctival nodules iris nodules vitreous opacities retinal and optic disc changes appeared to be typical Earlier histological studies have shown that any part of the eye or its adnexa can contain epithelioid cell granulomas (Zimmerman & Maumenee 1961 Gass & Olson 1973 Thiel & Korenke 1975) In the present study epithelioid cell granulomas were verified histologically from conjunctivae and the lacrimal sac

However the morphological and histological sarcoid changes of the eye and its adnexa are not pathognomonic to the disease since a granulomatous reaction e g to bacteria fungi or foreign bodies can cause similar biomicroscopic changes or a similar epithelioid cell formation in a histo logical section (Villar 1977) In the differential diagnosis of uveitis be lieved to be due to sarcoidosis the possibility of haematogenous tuberculosis should not be overlooked However tuberculous nodular iritis is probably rare in Finland since no instance was seen during the years covered by the present study All the cases of nodular iritis were of sarcoid etiology In one patient (Case 6 Table X) the nodular iritis was at first believed to be caused by tuberculosis since no other manifestation of sarcoidosis could be shown and the tuberculin test with 1 TU was positive During the follow up period however the patient developed gener alised sarcoidosis (see page 83 for the case report)

Ophthalmic changes as part of systemic disease Sarcoidosis is a systemic disease and this was one of the criteria of diagnosis The ophthalmic manifestations in the present series were always at some stage of the disease accompanied by at least one other manifestation of sarcoidosis The patients with chronic uveitis had particularly many other forms of the disease whereas sarcoidosis of the conjunctivae or the lacri

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mal glands could appear as the only sign in addition to lung affection On the other hand reduced lacrimal secretion and conjunctival granulomatosis were often associated with sarcoid skin lesions This latter correlation has been reported already earlier (Blegvad 1931 Krummel 1953) The common ectodermal origin of the skin, conjunctiva and lacrimal gland might possibly explain why they are readily affected in one and the same subject with this disease

Erythema nodosum occurred in about a quarter of the present series In patients with erythema nodosum, however, the rate of ophthalmic manifestations was lower than in patients with joint, parotid or neurological changes or especially in those who had cutaneous lesions peripheral lymphadenopathy or hypercalcaemia The observations are compatible with the knowledge that erythema nodosum in sarcoidosis is often a sign of a restricted, transient form of the disease (Lofgren 1953b Scadding 1967)

Only one of the 79 patients in whom ophthalmic sarcoid changes were found, presented no radiological lung changes even during the follow-up period Three patients with uveitis had no lung changes at the time of the manifestation of uveitis, but two developed them one 3 1/2 years and the other 10 years after the onset of uveitis Lung changes are known either to precede or succeed uveitis (Smellie & Hoyle 1960 Rudberg-Roos 1962) According to Siltzbach (1967b) a resolved chest radiograph in a patient with sarcoidosis is usually a sign of a relatively late phase of the disease The fact that in the series reported on by James et al (1964) more than a quarter of the patients with sarcoid uveitis had radiologically unaffected lungs may therefore indicate that the series contained many chronic cases The present observation that conjunctival granulomas were found in patients with a resolved chest radiograph (see Table XIX) was a sign that the disease continued and was thus compatible with Siltzbach s (1967b) assumption referred to above

VI SUMMARY AND CONCLUSIONS

The purpose of the study was to outline the ophthalmological aspects of sarcoidosis and to ascertain the other manifestations of the disease in the same patients Special attention was devoted to the uveal and conjunctival changes and the lacrimal gland function

The series of 281 patients was composed of all the patients with sarcoidosis examined and histologically confirmed at the Oulu University Central Hospital and at Paivarinne Hospital in 1971—77 Every patient underwent a thorough ophthalmological examination including Schirmer s test and examination of the fundus with a three mirror contact lens A biopsy for histological examination was taken from the conjunctiva of 218 patients The characteristics of uveitis were studied by iris fluorescein angiography iris infrared transillumination photography and retinal fluorescein angiography

Ophthalmic changes were the most frequent among the extrathoracic manifestations of sarcoidosis They were found in 79 patients of the series (28 1 %) The most common among them was conjunctival sarcoidosis (17 0 %) followed by reduced lacrimal secretion (12 6 %) uveitis (7 8 %) and band keratopathy (3 9 %) The last mentioned was associated with an elevated serum calcium level

Ophthalmic manifestations were always accompanied by one or several other manifestations of sarcoidosis Non-ophthalmic changes were more numerous in patients with chronic than acute uveitis Conjunctival and lacrimal gland sarcoidosis were accompanied by sarcoid skin lesions in almost half of the patients One-third of the 66 patients with erythema nodosum had ophthalmic changes These changes were more common in patients who had joint, parotid or neurological affections cutaneous lesions peripheral lymphadenopathy or hypercalcaemia 15 cases of the present series were classified as Heerfordt s syndrome

Uveitis was almost always bilateral (20/22) and generalised (21/22) and in the vast majority of cases (17/22) occurred in women Taches-de bougie exudates and nonspecific chorioretinitis were the most common

mal glands could appear as the only sign in addition to lung affection On the other hand reduced lacrimal secretion and conjunctival granulomatosis were often associated with sarcoid skin lesions This latter correlation has been reported already earlier (Blegvad 1931, Krummel 1953) The common ectodermal origin of the skin, conjunctiva and lacrimal gland might possibly explain why they are readily affected in one and the same subject with this disease

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VII CASE REPORTS

Case 1 (Table XV) A 40 year old car driver who had earlier been healthy fell ill in August 1966 Both of the parotid glands and the lacrimal glands suddenly became swollen and his eyes felt dry The saliva ceased to flow and he had a bad taste in his mouth. A fortnight later he contracted a minipapular rash hard subcutaneous nodules appeared on the arms and the cutaneous scars grew in size and became red The salivary gland swelling which was first thought to be mumps and the lacrimal gland swelling disappeared in a month, and the symptoms of dryness of the eyes became milder but the cutaneous changes persisted for several months

In December 1966 both eyes gradually became painful and the visual acuity impaired. Because of dilated pupils not reacting to light the patient was sent for a neurological examination Apart from the pupillary finding the neurological status was normal The cerebrospinal fluid however contained some lymphocytes and slightly elevated total proteins Intraocular hypertension was suspected and an ophthalmological examination in January 1967 revealed hypertensive uveitis (Case 14 Table X) large stiff pupils subepithelial corneal oedema fine keratitic precipitates and weak aqueous flare with few cells Intraocular pressure was 55 mmHg in the right and 69 mmHg in the left eye Chest radiography revealed bilateral hilar adenopathy Not until this stage six months after the first symptom was sarcoidosis suspected and the diagnosis was confirmed by histological examination of a biopsy specimen of a scar and by a positive Kveim test The tuberculin test with 1 TU was negative but with 10 TU positive

The intraocular pressures were restored to normal within a few weeks the inflammation subsided with topical and systemic corticosteroid treatment. In the acute phase the patient was also given acetazolamide The uveitis did not recur In the left eye the pupil remained larger and stiffer than in the right. Slight atrophy persisted in the iris as did a few anterior synechiae chorioretinitis and taches de bougie formations left peripheral fundus scars and a paracentral defect remained in the visual field The lacrimal gland function was restored and the chest radiograph became normalised The patient still showed symptoms of peripheral neuropathy attributed to sarcoidosis at the end of the present study period

Case (Table XV) A 48 year old worker's wife who had cardiac insufficiency and impaired peripheral circulation, became ill in March 1974 there was enlargement of the right parotid gland slightly impaired vision of the right eye and a feeling of dryness in both of the eyes and the mouth The parotitis healed in two weeks. In September 1974 the patient's right eye became photophobic and in November 19 4 visual acuity deteriorated considerably Ophthalmological

among the fundus changes Retinal granulomas were observed in two patients, one of whom also had optic disc granulomatosis

In more than one-third of the cases of uveitis corticosteroid therapy given to all patients with uveitis failed to lead to a definite recovery, and in an equal proportion the uveitis led to some degree of permanent impairment of visual acuity One uveitic eye was blinded as a result of phthisis

Fluorescein iris angiography showed more granulomas than was seen in biomicroscopy and was also able to differentiate between fresh and old granulomas The fluorescein angiogram of the retinal and optic disc granulomas had an appearance similar to that of iris granulomas The infrared transillumination technique revealed the defects in pigment epithelium produced by nodules especially in the pupillary area

Conjunctival biopsy showed epithelioid cell granulomas compatible with sarcoidosis in 40 9 % of those in whom it was suspected on the basis of biomicroscopic appearance In the diagnosis of sarcoidosis, conjunctival biopsy as part of the ophthalmological examination is a procedure to be recommended before more demanding methods are tried

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Ophthalmic manifestations in sarcoidosis in common with sarcoid lesions elsewhere in the organism, are characterised by a scarcity of symptoms not in proportion to the finding

The ophthalmic changes in sarcoidosis frequently present a typical appearance in slit-lamp examination

Heerfordt s syndrome is seldom complete It cannot be diagnosed until the course of sarcoidosis has been observed for a sufficiently long time because the symptoms making up the syndrome do not always occur simultaneously

Conjunctival and lacrimal gland sarcoidosis seem to be considerably more frequent ophthalmic manifestations than uveitis

The prognosis of sarcoid uveitis is uncertain In a considerable number of cases, the uveitis leads to permanent impairment of the visual acuity

Conjunctival biopsy is an important diagnostic method Its great advantage for both the patient and the doctor is the ease with which it can be performed

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examination revealed retinal detachment in the right eye caused by a hole produced by perivasculitis and traction and a mild panuveitis in both eyes (Case 16 Table X) The periphery of both eyes showed taches-de-bougie exudates The lacrimal secretion was found to be reduced

The chest radiograph was suggestive of a II° sarcoid change The diagnosis of sarcoidosis was confirmed by a lymph node specimen taken by mediastinoscopy Tuberculin test with 10 TU was negative A successful plombage operation was performed on the right eye but the vision remained poor since the macula had been detached Lacrimal secretion remained low After a follow up period of 3 1/2 years the peripheral uveitis was still active and required treatment

Case 3 (Table XV) A farmer s wife aged 40 who had earlier been well acquired left facial palsy in November 1973 and a fortnight later right facial palsy Simultaneously she had frontal headache a feeling of numbness in the face in different parts of the body and in the palate impairment of the sense of taste and of smell difficulty in swallowing and weakness in the lower extremities The eyes and the mouth felt dry

Ophthalmological examination revealed a mild uveitis of chronic appearance in both eyes (Case 18 Table X) a slight aqueous flare in both eyes anterior and posterior synechiae tiny woolly exudates around the peripheral vessels of the fundus and small peripheral areas with chorioretinitis The lacrimal secretion was reduced

Cerebrospinal fluid contained an excess of cells and the proteins were slightly elevated The etiology of the disease remained uncertain Systemic corticosteroid treatment relieved the symptoms and was continued for six months In September 1974 after corticosteroid therapy had been discontinued the patient experienced a feeling of tightness pain and weakness in both upper and lower extremities which locally became hard and thickened At the same time the parotid glands hardened and became enlarged and the eyelids were swollen The symptoms of dryness of the mouth and eyes worsened Purple patches appeared on the skin of the legs Uveitis showed no signs of activation Sarcoidosis was suspected and the diagnosis was histologically confirmed by a sample taken from the swollen biceps brachii muscle Tuberculin test with 1 TU was negative but with 10 TU positive No radiological changes were observed in the lungs during the four years of follow-up

With another course of systemic corticosteroid therapy most of the symptoms subsided within a year leaving behind mild neurological defects A maintenance dose of 10 mg prednisolone a day was continued after the termination of the period of the present study

Case 1 (Table X) A 34 year old mental hospital nurse suffered from chronic allergic rhinitis chronic sinusitis asthma and psoriasis She had a high degree myopia Since 1967 she had been affected with chronic uveitis of unknown etiology of the left eye In January 1976 erythema nodosum patches appeared on her legs healing within a couple of months At the same time hilar gland hypertrophy and parenchymal changes were observed in chest radiography Lymph node biopsy by mediastinoscopy confirmed that they were compatible with sarcoidosis Tuberculin test which had earlier been positive to 1 TU changed to negative Six months later the uveitis of the left eye became exacerbated In this connection slightly elevated light grey botryoid lesions were observed in the left retina inferotemporally to the macula With topical and systemic

corticosteroid therapy the lesions disappeared in six months without pigment formation The vision of the left eye was permanently impaired due to the cystic macular oedema occasioned by the chronic uveitis

Case 6 (Table X) A tuberculosis-sanatorium nurse aged 42 suffered from hypertension and cardiac insufficiency She consulted the outpatient eye clinic in April 1975 because of slight aching and reddening of the left eye with floating flakes in the field of vision. She had had the symptoms for four months A monocular granulomatous uveitis was found with large nodules on the iris (Fig 7) large snowball like opacities in the vitreous peripheral chorioretinitis foci in the fundus and vasculitic changes in the vessels (Figs 14 A 14 B)

Since the chest radiograph did not differ from normal while the tuberculin test was positive even to 1 TU and there had been pronounced exposure to tuberculosis, the etiology was considered tuberculous However TB cultures from the sputum and urine were repeatedly negative

The patient was given not only systemic and topical corticosteroid treatment but also antituberculous drugs The corticosteroid therapy was continued for six months but after it had been stopped the uveitis again became active Fresh nodules began to appear on the left iris and the vitreous opacities increased In this connection purple plaques developed on the skin of the legs and back A biopsy specimen was taken and revealed granulomas of epithelioid cells compatible with sarcoidosis.

Three and a half years later sarcoidosis was manifested also with lung changes Associated with this activation nodules appeared again on the left iris a granuloma also in the left optic disc and another over the lower temporal vein of the retina (Figs 17 A 17 B 17 C) In addition fresh foci appeared along the periphery of the retinochoroidal scar areas Despite the optic disc changes the vision of the left eye remained intact

Case 4 (Table X) A 19 year old student, previously healthy in October 1974 suffered a right facial palsy which subsided within five months A month and a half after the onset of the facial palsy he experienced mild eye trouble reddening and reduced visual acuity in both eyes in the morning An ophthalmological examination was made two months after the onset of symptoms Granulomatous uveitis was diagnosed in both eyes In the left iris there were two large yellowish red granulomas, one of them covering the entire radius of the iris (Fig 5) An intense vitreous reaction was seen. Chest radiography revealed hilar gland hypertrophy The tuberculin test was negative to 100 TU Histological confirmation of sarcoidosis was obtained by liver biopsy

For almost a year it seemed that the uveitis could be controlled by topical and systemic corticosteroid therapy but the inflammation then developed into an exudative-fibrous process which, as a result of secondary glaucoma and cataract and of the attempts at treating them, led to a phthisis of the left eye less than a year later (Fig 6) At the end of the present study period, that is three years from the onset of the uveitis the disease was still active the aqueous flare was intense and there were pressure difficulties in the fellow eye the vision of which was also threatened.

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The present study was carried out at the Oulu University Central Hospital Department of Ophthalmology, in 1971—1977 I am grateful to my esteemed teacher and former chief, Professor Henrik Forsius, M D, for having granted me the privilege of using the excellent facilities of his department, and for his friendly support in all the various phases of this work

My particularly warm thanks are due to Associate Professor Esko Huhti, M D, under whose guidance the examination and treatment of the patients with sarcoidosis took place at our hospital He followed my work and encouraged me from the very beginning, helped me to plan the study, interpreted the chest radiographs and gave wise advice concerning the manuscript

I cordially thank Docent Leila Laatikainen, M D, for her thorough familiarisation with the manuscript for stimulating discussions concerning the interpretation of angiographs and for the many constructive suggestions she made

My father, Professor Sakari Vainio M D, made a valuable contribution by revising the first draft of the manuscript This greatly clarified my thoughts and brought the work a decisive step forward My fondest thanks are due to him

I have a particularly warm regard for the nursing personnel of the Department of Ophthalmology of Oulu University Central Hospital They were always ready to give a helping hand in the many practical problems connected with the study Similarly, I owe a debt of gratitude to my colleagues for their positive attitude throughout all phases of the work

Docent Seppo Sutinen, M D interpreted the histological findings of the conjunctival biopsies and familiarised me with the histopathology of sarcoidosis I am very grateful for this extremely valuable help

I am also greatly indebted to Mr Heikki Nieminen for the innumerable photographs he took to supply an essential part of the work and to Mrs Seija Nieminen for her skilful drawings

In addition, I offer grateful thanks to Dr Martti Saloheimo M D Head of the Paivarinne Hospital who allowed me to examine his patients and made patient data available to me to Dr Seppo Lahde M D for interpretation of bone radiographs to Mr Raimo Salo for the computerisation involved to Mrs Pirkko Orell for collecting the necessary literature and to Mrs Aino Nikupaavo M A for checking the bibliography

Mrs Hilkka Kontiopaa M A and Mrs Barbara Rikberg undertook responsibility for the English version of the manuscript I am very grateful to them and also to Miss Heli Aspelin who competently typed the manuscript

My warm thanks are also due to all the patients included in my series

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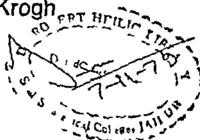
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The Corneofundal Potential and the Electrooculogram

Aspects of Normal Physiology and Variability

by

Erik Krogh



SCRIPTOR COPENHAGEN 1979

Forsvaret finder sted fredag den 22 juni 1979 kl 14 00 præcis
i Panumauditoriet Panuminstituttet Blegdamsvej 3 B 2200 Kobenhavn N

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PREFACE

The following pages survey the centenary history of the efforts concerned with developing the recording of the corneofundal potential in animals and human beings

The author s contribution to this field was carried out in the years 1973–1975 in the University Eye Clinic Rigshospitalet Copenhagen My sincere thanks are due first of all to Professor Eilif Gregersen M D head of the Clinic for his never failing interest and support from the planning phase to the conclusion of my study Likewise I am greatly indebted to Professor Ove Sten Knudsen M D Department of Biophysics University of Copenhagen He made it clear to me that a clinical approach to electrooculography without some foundation of basic physics and amplifier technology would entail a substantial risk of superficiality and guided me accordingly throughout the whole of my work

Also I owe my thanks to the engineers Knud Dahl Department of Clinical Neurophysiology Rigshospitalet Copenhagen and Hans Nissen Petersen Department of Biophysics University of Copenhagen for careful instruction and great practical help Jørgen Nyboe actuary and Ulla Grohn B Sc both from the Department of Statistics Rigshospitalet Copenhagen spent much of their valuable time with discussions of the statistical and datalogical aspects of my investigations and gave me access to the electronic data processing facilities of the department

Jens Edmund M D consultant at the University Eye Clinic Rigshospitalet Copenhagen endowed me with his warm enthusiasm in prolific as well as in stagnant periods and I gratefully look back upon many enlightening discussions on methodological problems with my colleagues Poul Helge Alsbirk Hans Fledelius Ole Nissen Jan Ulrik Prause and Munthe Suenson

During the years 1973–1975 I held a research fellowship from the University of Copenhagen Further grants were obtained from P Carl Petersens Fond« and from Cykelhandler P Th Rasmussen og hustru Alma Rasmussens Mindelegat the last mentioned kindly effected by the Committee for the Prevention of Blindness In my subsequent appointment at the Institute of Eye Pathology University of Copenhagen Sigurd Ry Andersen M D head of the Institute offered me excellent and inspiring working conditions for the completion of the statistical analysis and the manuscripts

Kirsten Helbech Margit Johannessen and Irene Sorensen medical secretaries typed the many preliminary and the final version of this survey

Denne afhandling er i forbindelse med omstående tidligere publicerede afhandlinger af det lægevidenskabelige fakultet ved Københavns Universitet antaget til offentlig at forsvares for den medicinske doktorgrad

København den 14 marts 1979

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I Krogh E (1975) DC recording of the human corneofundal potential Albrecht v Graefe s Arch klin exp Ophthal 193 205–215

II Krogh E (1975) The corneofundal potential of the rabbit eye An assessment based on Thévenin s theorem Ophthal Res 7 236–245

III Krogh E (1975) Normal values in clinical electrooculography I Material method methodological investigations and distribution of the potential and time parameters Acta ophthal (Kbh) 53 563–575

IV Krogh E (1976) Normal values in clinical electrooculography II Analysis of potential and time parameters and their relation to other variables Acta ophthal (Kbh) 54 389–400

V Krogh E (1977) Normal values in clinical electrooculography III Numerical evaluation of two dimensionless EOG parameters Acta ophthal (Kbh) 55 227–236

VI Krogh E (1977) Normal values in clinical electrooculography IV Analysis of two dimensionless EOG parameters and their relation to other variables Acta ophthal (Kbh) 55 739–749

VII Krogh E (1977) Normal values in clinical electrooculography V Variability within and between eyes Acta ophthal (Kbh) 55 986–993

Lastly, I have to apologize for the recurring periods of absent mindedness, which this study has brought about Fortunately, family, friends and colleagues seem to come of sturdy stocks

April 1979,
Erik Krogh

INTRODUCTION

In 1849 du Bois Reymond measured a potential difference of 6 mV the cornea being positive between the anterior and posterior poles of an enucleated tench eye

Holmgren (1865 1871) confirmed that a similar potential existed in the frog and was further able to show that it underwent rapid changes later to be known as the electroretinogram (ERG) in reaction to changes in illumination intensity He also found that a potential difference of almost the same magnitude as in the intact eye bulb existed between an electrode in the vitreous body and another on the scleral surface of an equatorially bisected frog eye Dewar (1877) examined the light induced oscillations in human beings but was disturbed by artifactual potential changes which he traced to the inevitable movements of the eye under investigation Fifty years later Schott (1922) realized the possibility of recording eye movements by means of the accompanying changes in the periorbital potential field and this particular technique has since developed into a valuable tool in otoneurological diagnosis under the title of electronystagmography (ENG)

In 1954 Riggs published an investigation of the ERG in night blindness of varios etiologies Three cases of retinitis pigmentosa all showed a reduced scotopic b wave but in addition a striking reduction of the ENG potential level was noticed in the most severe case This result was confirmed by François & de Rouck (1955) who shortly after presented the first systematic investigations of the magnitude of these potentials recorded from both normal and pathological eyes (François et al 1955 1956a 1956b 1957) Further methodological advances were introduced by Arden & Kelsey (1962a 1962b) and Arden et al (1962) and since then numerous reports concerning the diagnostic and prognostic value of such recordings in ophthalmology have emerged Comprehensive surveys of the clinico pathological literature are given by François et al (1974) and Kolder (1974) The older literature – mainly dealing with animal experiments – is reviewed by Kohlrausch (1931)

The present paper consists of a survey of the earlier literature concerning the corneofundal potential and of an account of the author s investigations of its normal physiology and variability in direct recordings from the rabbit eye and indirect recordings from healthy human beings In the latter a direct coupled (DC) amplification has been used instead of the conventional condensor coupled (alternating current AC) signal transfer in accordance with the author s comparative study of the accuracy and precision connected with these procedures Special attention is given to the various standardized recording and

CONTENTS

RECORDING PROCEDURES

Two essentially different methods of recording the CFP can be adopted
1) a direct measurement by means of electrodes placed at the anterior and posterior poles of the eye the posterior electrode sometimes being transferred to some other part of the body The latter modification introduces a bias in the quantitative CFP estimation but may be perfectly adequate for qualitative statements
2) an indirect recording whereby suitably placed electrodes pick up the changes in the periorbital electric field produced by eye movements The resulting voltages represent only a fraction – more or less constant – of the CFP

Direct recording

The polar placement of electrodes on an enucleated eye was used by du Bois Reymond (1849) Holmgren (1865 1870–71 1880) Kuhne & Steiner (1881) Gotch (1903) Waller (1905) Piper (1904 1911) Muller Limmroth & Lemaitre (1953) and Muller Limmroth (1955) This procedure is feasible with eyes from cold blooded animals only as the CFP of a warm blooded species disappears rapidly after enucleation of the eye (Dewar 1877 Krogh II) Direct in situ recordings with one electrode on the cornea and the other on the brain skin conjunctiva the retina or in the orbit have been accomplished among others by Dewar (1877) Kikawada (1968) Mita et al (1969) Gouras & Carr (1965) and Ulrich et al (1972) Operative exposure of the posterior part of the eye has been attempted by Dewar (1877) Brossa & Kohlrausch (1913) and Noell (1952)

A direct recording of a human CFP was apparently first attempted in auto-experiments by Sachs (described by Kohlrausch 1931) who used gelatine electrodes placed at the limbus and in the temporal region respectively No systematic changes in the irregularly changing voltage could be evoked The same conclusion is reached in the case of the technique of Dunn et al (1969 1974) which did not even allow ERG recordings of good quality to emerge from the hand held calomel electrodes Skoog (1975) employed a suction contact lens and a frontal reference electrode connected to matched temperature stabilized calomel half-cells He obtained accurate recordings of the CFP potential variations accompanying changes in illumination intensity closely corresponding to previous experience with the indirectly recorded CFP

Indirect recording

The electric registration of human eye movements was established by Schott (1922) He was not interested in the potential itself which he considered to be

evaluation practices which have been designed with the aim of obtaining information for the solving of clinical problems However, the earlier investi gations contain no reasonably large and representative normal samples, in which the possible relations between the indirectly recorded corneofundal potential and other variables of the eye or the subject could be studied Therefore the author decided to collect such a sample and make it a subject of a statistical analysis with the purpose of procuring some well founded norma tive figures for the continuing clinical exploitation of this branch of ophthal mophysiology

DEFINITIONS AND ABBREVIATIONS

The corneofundal potential (CFP synonyms resting potential standing po tential corneoretinal potential Bestandpotential Ruhestrom) is the voltage found between the anterior and posterior poles of the eye This exhibits specific slow changes in reaction to alterations of the intensity of the light impinging on the retina *The electroretinogram* (ERG) is a fast polyphasic potential oscillation evoked by a sudden light stimulus usually a flash and superimposed upon the CFP

In *electrooculography* (EOG) eye movements cause a part of the CFP to be picked up by periorbitally situated electrodes and the resulting potential time curve is called an *electrooculogram* (EOG) The supplementary term »clini cal« signifies that the recording procedure is standardized in order to obtain information about the functional state of the photosensitive and associated layers of the eye

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generated by mechanical phenomena Mowrer et al (1936) provided the neces sary link between the CFP and eye movement potentials by demonstrating among other things that active and passive movements of the cat eye produced essentially identical recorder deflections without any resemblance to an elec tromyogram and that the deflections gradually disappeared after injection of chromic acid into the vitreous space Since then Schott s method has been used extensively in study of the CFP without essential modification Heck & Papst (1956) developed a technique, based on passive rotation by means of sutures stitched to the eye for use in animal experiments which has since been used in more or less modified forms by numerous workers (Horsten et al 1963, Pasik et al 1965, Arden & Ikeda 1966, Foulds & Ikeda 1966, Kolder & North 1966)

Indirect CFP recording contains however several particular problems, which will be discussed in the following paragraphs

It is natural to ask how the recorded potentials are related to the angular excursion of the eye although the answer is of little consequence to the clinical EOG which is based on the recording of basically equidistant saccades There are theoretical reasons to expect a sine relationship and this also has been demonstrated (Fenn & Hursh 1937 Mackensen & Harder 1954) On the other hand Leksell (1939) was able to show that for excursions of up to 45° from the median plane the potentials may be considered as directly proportional to the angle

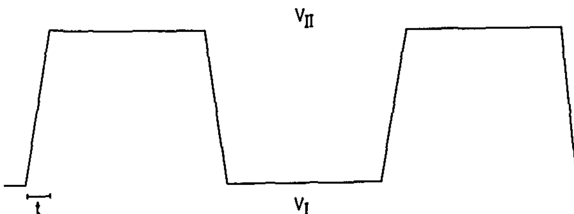


Fig 1 The electrical display of saccadic eye movements between two fixation marks as picked up by periorbital electrodes in the plane of the movement V_I and V_{II} represent the EOG voltage values in the two resting positions of the eye t is the time in which one saccade is completed = the rise time of the signal

Another important question is whether the CFP is reduced by a constant factor when repeated recordings are carried out Fig 1 shows a recording under optimal conditions of rhytmically performed saccades between two fixation points The black line represents the potential difference between two electrodes situated in the periorbital region in the plane of the eye movements In the first position the recorded voltage (V_I) is composed of a fraction of the CFP ($k_1 \times$ CFP) plus contributions from other biological voltage sources and from the skin-electrode contact (off set) In the second position V_{II} consists of another fraction of the CFP ($k_2 \times$ CFP) plus the contributions mentioned above Electrode potentials are however slowly changing or stable and so is the resistance of the skin (Wang 1957 Geddes & Baker 1968) and consequently they will contribute very little to the difference between V_I and V_{II} since the saccade is carried through in a fraction of a second Then

1) $V_I - V_{II} = (k_1 - k_2) \times CFP = k_3 \times CFP$

which means that the recorded CFP is independent of other voltage sources producing a steady or slowly changing voltage (structures such as the jaw musculature and the levator palpebrae (Ford 1959) occasionally produce rapid potential changes (spikes) which do not however change the level of V_I and V_{II} and therefore do not disturb the reading) On the other hand these voltage sources can disturb the recording by their capacity to induce a base line drift which if not controlled may necessitate electric filtering of the signal (see below)

The factor k_3 depends on the distance between the voltage generator and the electrodes and on the conductive character of the tissues through which the current travels before being picked up by the electrodes The distance factor has been investigated by Mackensen & Harder (1954) but the complex volume conductor properties of the head escapes any practical quantification Thus a constant proportional ty factor from person to person from trial to trial and even during an ordinary clinical EOG recording in one person cannot be taken for granted

The electrode resistance is in series with the voltage source and will not diminish the EOG potential provided the input resistance of the recorder is sufficiently high On the other hand a major difference between the two electrode resistances diminishes the rejection of noise signals common to both pick up regions (mains) A minimal *difference* between two electrode resistances is best obtained by making them both small

The first electric registration of eye movements was performed with a directly coupled galvanometer (Schott 1922) but most later investigations of EOG potentials have employed signal filtering amplifiers This means that only frequencies within certain limits (the bandwidth) pass the amplifier input

without being seriously attenuated This is done in order to diminish noise signls from the measuring object (large DC levels high frequency voltages from other electric equipment) and the noise inherent in the amplifier circuit The two frequencies in the bandwidth specification signify that the attenuation factor has reached $\frac{1}{\sqrt{2}}$, and increases steeply outside the frequency span The frequencies are related to the time constant of the filters by the following equation

2) $\tau = \frac{1}{2\pi f_L}$, where f_L is the upper or lower cut off (limit) frequency

Regarding the upper cut off frequency, it is safe to use a time constant of 1/10 of the smallest time interval necessary for a faithful reproduction of the information in question (Sten Knudsen & Nissen Petersen 1971) An EOG trace is usually displayed by a 0 5 Hz frequency, and theoretically it could be high frequency filtered to such a degree that the correct V_I and V_{II} levels

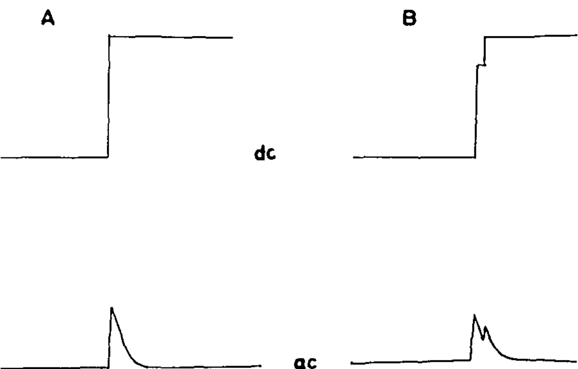


Fig 2 A regular (A) and irregular (B) saccade depicted by a DC operated amplifier (upper part) and by an AC operated amplifier with a small time constant (lower part) The amplitude loss inherent in the AC technique is illustrated together with the supplementary distorsion of an irregular saccade

would be reached at the end of the 1 s fixation pauses For measuring pur poses a more ideal curve results if the filter allows the rapid shifts between V_I and V_{II} to be depicted accurately leaving fixation plateaux of approxi mately 1 s This rise time (t in Fig 1) depends upon the velocity of the saccade and according to the somewhat conflicting literature on this subject (Dodge & Cline 1901 Dodge 1903 Miles 1929 Brockhurst & Lion 1951a 1951b Mackensen 1958 Kris 1960 Aantaa 1970 Boghen et al 1974) a certain inter and intraindividual variation of the velocity of a specified angular excur sion influenced by among other things fatigue and sleepiness must be ex pected Accordingly the duration of a 30° saccade should vary between 0 1 and 0 5 s In the case of the high frequency filter the smallest value must be used in calculating the cut off frequency The appropriate time constant being 0 01 s the upper cut-off frequency must be 16 Hz according to formula (2) With this filter specification mains pick up and of course higher frequencies are effec tively damped

The most conspicuous effect of filtering-off the steady state or low frequency voltages (AC or alternating current technique) is that in the event of an unchanged input voltage the displayed trace cannot be kept at a constant level but converges towards the base line which is in practice reached within an interval of 5 time constants This means that an EOG recording such as that in Fig 1 is converted into a train of saw tooth figures or even spikes (Fig 2) A more serious consequence is that a low frequency filter inevitably introduces an amplitude loss of a ramp or trapez signal which depends on the magnitude of the time constant (greater with smaller time constants) and of the rise time In the case of the EOG signal the rise time cannot be considered constant (see above) and accordingly its influence upon the amplitude loss should be elimi nated or at least kept acceptably small If the amplitude loss should not exceed 1% the time constant should be at least 50 times the largest rise time in this case 25 s (Sten Knudsen & Nissen Petersen 1971) Such filter specifications are not generally available in biomedical amplifiers and furthermore would involve a time-consuming mode of operation if not alleviated by extra elec tronic short circuiting possibilities Finally irregularly performed saccades can only be measured accurately in a DC operated display (Fig 2)

A priori a direct current (DC) amplification of the EOG signal with no low fre quency filtering therefore appears to be preferable

AUTHOR'S INVESTIGATIONS (I)

An essential feature of EOG potentials is their great variability (François et al 1955 1956a 1956b 1957 Shackel 1960 Shackel & Davis 1960 Davis & Shackel 1960 Arden et al 1962 Arden & Barrada 1962 Gliem 1971) The

reasons for this include the CFP changes induced by varying lighting condi tions, to which proper attention is not always given particularly by non ophthalmological investigators, differing electrode characteristics and placements and too small an input resistance in the galvanometers employed in earlier investigations As already mentioned the conventional AC registration with marked low frequency filtering (small time constant) allows for the influ ence of the eye movement velocity upon the recorded amplitudes The present investigation was undertaken in order to assess the importance of this factor and to try to standardize a DC recording of the human CFP by means of commercial electrode and amplifier/display equipment This involves a test of the electronic equipment and the electrodes, notably their drift and noise characteristics in simple set ups and connected to the actual measuring object Also, the effect of more or less vigorous preparation of the skin contact areas are investigated, and simultaneous AC/DC measurements will be performed under conditions similar to those of a clinical EOG recording

MATERIALS AND METHODS

Members of the staff and patients from the Department of Ophthalmology Rigshospitalet were used as test subjects Persons with bad fixation or sus pected of a decreased CFP were not included

The electronic recording and testing equipment consisted of a Mingograph (Siemens type M34) provided with EMT 12 B pre amplifiers (input resistance 50 MΩ nominal common mode rejection ratio 10 000 1 range of upper cut off frequencies 15–700 Hz range of lower cut off frequencies 0–27 Hz (time constants from ∞ to 0 059 s)) an oscilloscope (Advance type OS 2000) a digital multimeter (Philips type PM2421), a sweep generator (Exact, type 127 B) cup shaped silver silver chloride electrodes (Beckman) and flat lead alloy electrodes (Kaiser)

RESULTS

Various filter combinations of the Mingograph were tested with sinusoidal step and ramp pulses which were attenuated according to the specifications The base line drift inherent in the amplifier was very low (8–10 μV/h) and the noise level was also sufficiently low (a pattern of irregular waves with peak to peak voltages corresponding to a 2–6 μV input)

The two electrode types were investigated in pairs The off set potentials were measured first in a physiologic saline solution The off set potentials could be diminished considerably by not using new or thoroughly cleaned specimens and by storage in physiologic saline for some hours with shortcircuited leads A

far less off set was obtained when the appropriate jelly or paste made up the conducting medium particularly in the case of the lead electrodes The resistance of the electrode pairs was 200–400 Ω again in the case of the latter type provided un impregnated specimens were not used In a solution of saline neither of the two electrode types showed any sensitivity to flashes of light nor was the drift rate altered by sustained illumination Mechanical actions such as movement of the skin beneath the electrodes caused only temporary disturbances of the recording in the form of smooth deviations or spikes not to be confused with the EOG signal Tapping the electrodes or pulling the leads induced a drift sometimes of long standing in recordings with the lead electrodes whereas the cup electrodes were almost insensitive to such handling

The way in which the electrodes were stored between the sessions was of importance to the quality of the ensuing recording The silver silver chloride electrodes were best stored in dry state after gentle irrigation with warm saline whereas the lead electrodes were kept in pairs under slight pressure with bentonite paste interposed and with connected leads

The purpose of skin preparation at the electrode sites is to secure a small electrode skin potential difference – which is of particular importance in a DC recording – and sufficient rejection of noise signals common to both inputs of the amplifier (see above)

Experience shows that both aspects benefit in parallel from the procedure to be described A sequence of 1) abrasion of the horny scales of the epidermis 2) degreasing 3) imbibition with Ringer solution and 4) application of the relevant conducting medium caused the resistance in the measuring circuit to diminish from approximately 100 to 0 1–3 kΩ without appreciable further changes during 20 min of observation Also with good electrode fixation and cable connection the base line drift was small – 1–2° – and mostly controllable by the Mingograph s inherent small capacity of base line adjustment (DC compensation) Moreover with this small amount of drift the length of the displayed ramp could be considered a good approximation of the vertical distance between V_I and V_{II} given the paper speed and the rise time and provided excursions of at least 4 mm

Simultaneous AC/DC recordings were made of 30° saccades Three lower cut off frequencies corresponding to time constants of 5 1 2 and 0 15 s were employed the upper cut-off frequency being 15 Hz in all cases The AC recordings showed loss of signal amplitude in all cases varying from an average of 7% for the largest time constant to an average of 49% for the smallest time constant The differences in mean amplitude loss between each group of AC/DC combinations were statistically significant Simultaneous DC/DC registrations did not give rise to significant differences in amplitude Moreover

reasons for this include the CFP changes induced by varying lighting conditions to which proper attention is not always given particularly by non ophthalmological investigators, differing electrode characteristics and placements and too small an input resistance in the galvanometers employed in earlier investigations As already mentioned, the conventional AC registration with marked low frequency filtering (small time constant) allows for the influence of the eye movement velocity upon the recorded amplitudes The present investigation was undertaken in order to assess the importance of this factor and to try to standardize a DC recording of the human CFP by means of commercial electrode and amplifier/display equipment This involves a test of the electronic equipment and the electrodes, notably their drift and noise characteristics in simple set ups and connected to the actual measuring object Also, the effect of more or less vigorous preparation of the skin contact areas are investigated, and simultaneous AC/DC measurements will be performed under conditions similar to those of a clinical EOG recording

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Polarity, magnitude and surface distribution

In du Bois Reymond s measurements of the CFP (1849) the cornea was positive and the posterior pole negative The same polarity was found in the frog eye by Holmgren (1865 1871 1880) A reversed polarity was de monstrated in invertebrate eyes by Dewar & M Kendrick (1876) and Piper (1904 1911) and was explained by the latter author with reference to the different orientation of the visual cells

Du Bois Reymond measured a CFP of 6 mV in the tench eye The values found in the enucleated frog eyes vary between 2 and 12 mV (Holmgren 1865 1871 1880 Kuhne & Steiner 1880 Muller Limmroth 1955) Similar systematic in vestigations of eyes from warm blooded animals have not been presented because of the above mentioned difficulty in maintaining the CFP after enucleation Holmgren (1880) and Dewar & M Kendrick (1876) appear to have made a few trials with mammal eyes in situ but no figures were presented Noell (1952) found in rabbits a fairly constant CFP of 2 4 mV after exposing the eye from above and leaving it with intact sheaths and muscles

The potential distribution of the enucleated frog eye was studied by Holmgren (1880) and de Haas (1903) who found that the greatest potential difference existed between the corneal pole and a location half way between the ora serrata and the optic nerve in a few cases polar measurements gave rise to the highest figures Westerlund (1912a b) revised the earlier findings and intro duced corrections for the obvious time-dependent decrease of the CFP There after a monotonic potential increase was demonstrated when one electrode was placed at the corneal pole and the other moved along a meridian to the posterior pole Westerlund s own investigations confirmed this characteristic with the important addition that the CFP decreases immediately if the posterior electrode touches the optic nerve sheath These results were moreover sup ported by measurements on a mechano-electric eye model Although these findings suggest a radial (dipole) orientation of the CFP voltage generator no conclusion can be drawn from the surface potential distribution alone con cerning the magnitude and orientation of the internal potential generators (Helmholtz s theorem about current distribution in volume conductors (1853))

Origin of the corneofundal potential

Holmgren (1880) measured the potential difference between an electrode in the vitreous body and another on the posterior pole in the equatorially bisected frog eye He found a potential of the same polarity and almost the same magnitude as the CFP Waller (1905) considered the CFP to be an artefact due

there were also considerable differences in amplitude loss within each AC/DC combination although statistically significant in only two of the three groups Finally, when comparing the first half of the recording with the subject in dark with the second half in which a strong light stimulus was applied significant intra individual differences were found in some cases not varying systematically with the lighting conditions

DISCUSSION AND CONCLUSIONS

The present investigation has shown that reasonably up to date amplification equipment and proper attention to electrode and skin problems make possible a DC amplification of the indirectly recorded human CFP A clinical EOG test based on DC amplification, can easily be administered by the para medical staff The inter group variation of amplitude loss in the simultaneous AC/DC recordings of a 30° saccade is not surprising in view of the different time constants employed For the demonstrated intra group and intra individual variation, further explanation is necessary A decreased quality of the amplification and display of low frequency filtered signals is not a likely hypothesis The only signal parameter of importance to the difference between AC and DC registered signals is the rise time, which consequently cannot be considered sufficiently constant to allow a precise CFP estimate by means of AC amplification

Taking the 0 1–0 5 s range for the rise time as an exemplification, the amplitude loss in the present investigation could vary from almost zero (time constant 5 s) to 75% (time constant 0 15 s) (Sten Knudsen & Nissen Petersen 1971) These extreme values are not reached in the present study which probably means that the actual range of rise times is smaller

the intravenous injection of urethane The log stimulus response relation of both oscillations signified that the site of action is the light sensitive part of the eye

Other stimuli

The effect of cooling (Gotch 1904) polarization currents (Muller Limmroth & Lemaitre 1953) anoxia produced by raised intraocular pressure (Heck & Papst 1956 Mita et al 1969) and hypovolemic hypotension (Kolder & North 1966) have been studied Furthermore the actions of various chemical compounds have been investigated Mowrer et al (1935) found that intra vitreal injection of chromic acid caused an immediate reduction of the cat CFP Muller Limmroth & Lemaitre (1953) reported on the effects of strychnine urea and urethane Mita et al (1969) studied the effects of adrenaline and acetyl choline and further discovered that an intra carotidal injection of physiologic saline evoked a significant CFP rise unless performed very slowly

An important discovery was the demonstration of a large CFP rise following immediately upon intravenous injection of sodium azide in the rabbit (Noell 1952) By means of rather selective tissue poisons (iodoacetic acid and sodium iodate) the pigment epithelium was indicated as the probable site of action of the azide response The results were confirmed by Heck & Papst (1956) In rabbits with artificial retinal detachment the injection of azide causes a marked increase of the CFP even after elimination of all light induced potential changes provided the pigment epithelium remains histologically normal (Foulds & Ikeda 1966)

AUTHOR'S INVESTIGATIONS (II)

The present author s investigation was undertaken in order to measure the CFP and estimate its range of variation in living mammal eyes under well-defined and reproducible experimental conditions The large range of variation of the CFP figures in the investigations of cold blooded animals might be explained in part by e g differences in the length of time between enucleation and recording in humidity and temperature of the specimen and in the illumination circumstances Also the input resistance of the early galvanometers was rather low which means that current is drawn in an uncontrollable way from the object connected to the instrument However even in the case of a sufficiently high input resistance variations of the resistive properties of the measuring object may evoke fluctuations in the voltage readings It is true that when the input resistance is high enough the measured voltage will not be influenced by changes in a series-connected object resistance but it is important to realize that because of an inevitable surface current the eye bulb will act as a voltage divider with respect to the CFP and we may

to inevitable traumatization of the tissues This view became untenable how ever when Brossa & Kohlrausch (1913) succeeded in recording quite similar potentials from the frog s eye in situ

Investigations with rather selectively toxic agents (Noell 1952) as well as with micro electrode penetrations (Brown & Wiesel 1958) indicate the retinal pig ment epithelium as the site of origin of the CFP Also the isolated frog choroid pigment epithelium demonstrates a potential difference with the epithelial surface positive to the choroidal (Lasansky & de Fish 1966) Nevertheless the light induced *potential rise of the CFP appears to presume a* normal contact between the pigment epithelium and the visual cells (Arden & Kelsey 1962b Foulds & Ikeda 1966)

Although the main part of the CFP is generated in the posterior half of the eye small contributions from other parts of the eye cannot be excluded Lehmann & Meesmann (1924) claimed the Donnan potential between the blood and the aqueous to be the sole cause of the CFP – a view that was repudiated by the investigation of Muller Limmroth & Lemaitre (1953) Brindley (1956) meas ured a 70 mV difference between the interior and exterior of the frog lens and the rabbit lens and concluded that small differences between the anterior and posterior surface potentials were likely to contribute to the CFP In most of his experiments the lens nevertheless behaved like an equipotential surface Large potentials are produced in the ciliary body (Berggren *1960*) Membrane potentials of 50–70 mV exist in the corneal epithelium but the trans corneal potential measured with large electrodes is comparatively small (1–3 mV) (Kikkawa 1964 1966) Pasik et al (1965) made convincing indirect recordings of the monkey »EOG« after evisceration of the eye and implantation of a prosthesis in the scleral shell This suggests but does not prove the existence of scleral and/or extrabulbar contributions to the EOG recorded from intact eyes

Light induced changes of the animal corneofundal potential

Holmgren (1865 1871) discovered the polyphasic (ERG) potential oscillations occurring upon changes in illumination conditions Kuhne & Steiner (1881) and Brossa & Kohlrausch (1913) found that illumination of the frog retina also brought about a slow increase in the CFP Studies of higher vertebrates notably the rabbit have been carried out by Heck & Papst (1956) Horsten et al (1963) Kikawada (1968) François et al (1969) and Kolder & North (1966) the latter authors found that the CFP oscillations had two resonance frequen cies in the rabbit and the dog one produced by alternate light and dark phases *of 1 1 min duration* and another produced by 20 min phases in the rabbit and by 7 5 min phases in the dog The fast and slow oscillations reacted differently to

has not been subject to systematic investigations. A thorough analysis of this topic implies intra-ocular measurements of potentials and resistances by means of micro-electrodes which is outside the scope and possibility of the present investigation. Nevertheless the author found it worthwhile to present some simple calculations based upon experiments with macro-electrodes and let them throw some light upon this matter.

A simplified circuit diagram of the eye (Fig. 3) illustrates the problem. The voltage (V_M) which is measured between the poles of the eye depends upon the relation between the surface resistance (R_M) and the sum (R_S) of the remaining resistances in the circuit according to the formula

$$3)\quad V_M = EMF \frac{1}{1 + \frac{R_S}{R_M}}$$

This means that V_M is independent of changes in R_S only if $R_M >> R_S$. In the present investigation the levels of R_M and R_S will be assessed in order to obtain information about the significance of fluctuations of R_S for the CFP measurement: if – under comparable experimental conditions – a normal light induced CFP response and a large $\frac{R_M}{R_S}$ ratio together with a limited range of variation of R_S can be demonstrated, then the conclusions are that fluctuations in R_S does not influence the CFP in any measurable degree and that the light rise is caused by an increased EMF of the CFP generator. R_S will be assessed indirectly by measuring the internal resistance (R_i) of the specimen according to Thévenin's theorem (1883). The three resistances are related by the formula

$$4)\quad \frac{1}{R_i} = \frac{1}{R_M} + \frac{1}{R_S}$$

MATERIALS AND METHODS

Rabbits were chosen because of the absence of anterior ciliary arteries which means that the main part of the scleral surface can be cleaned of connective and muscle tissue without hindering the intraocular blood supply. In order to measure the CFP with the smallest possible surface current the eye was proptosed by means of limbal sutures and the scleral surface dried. In other experiments the eye was left in situ. The electrodes were of chlorided silver wire and they were checked for off set potential and DC resistance before each application.

assume that the current leak depends on the conducting properties of the *surrounding tissues and varies according to their amount of blood and ex* tracellular fluid The electromotive force (EMF) of the eye bulb is measured only when this current leak is zero in other cases the recorded CFP is a more or *less valid approximation to this parameter The present investigation therefore* seeks to determine the EMF of the rabbit eye with the best possible approxi mation The effect of increasing the surface current of the eye by different *means will also be studied in order to allow a gross quantitative estimate of the* degree of current shunting, when the eye is in its anatomical position

Usually, it is assumed that CFP variations following illumination shifts reflect changes in an intra ocular potential generator The alternative or supplemen tary hypothesis of a change in some resistive property of the specimen does not *find much support in theoretical considerations (Arden & Barrada 1962) and*

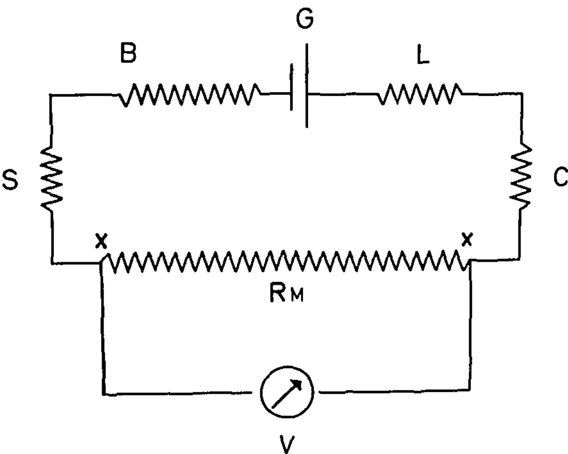


Fig 3 An electric equivalent diagram of the eye The potential generator in the pigment epithelium is denoted by G and L C S and B represent the tissue resistance corres ponding to the lens the cornea the sclera and Bruch s membrane The electrode contact is at x and R_M denotes the measuring (interelectrode) resistance

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RESULTS

The CFP of the proptosed and denuded rabbit eye varied between 11 and 20 mV, the cornea being positive After loading the specimen with a 1 kΩ resistor, the voltage drop corresponded to an internal resistance (R_i) of about 2 kΩ (range of variation 1 5–3 kΩ) Adaptation of the rabbit to dark and light elicited a fall and a rise respectively of the CFP The relative potential rise under light was greater than reported by François et al (1969), probably due to a slightly different illumination procedure R_i did not change appreciably during this procedure

In conformity with the hypothesis, considerable potential variations were elicited by increasing the conductivity of the scleral surface by wetting it or covering it with connective tissue Interruption of the blood supply tem porarily or by enucleation brought about a rapid reduction of the CFP Lessening of the input resistance of the recorder caused a drop in the CFP but no discernible changes of R_i were produced

Resistance measurements of corneoscleral shells established that R_M is 15–20 times greater than R_i, which means that R_s is practically equal to R_i (formula 4) The consequences are that the CFP readings of the proptosed eyes make up approximately 95% of the electromotive force and furthermore that fluctua tions of R_s at the actual level cannot account for the large span of CFP values

The estimated values of R_i and the peribulbar tissue shunt were used in a calculation of the CFP of the intact rabbit eye in situ The predicted values accorded well with the voltages measured in the closest possible approxima tion to the physiological state

DISCUSSION AND CONCLUSIONS

The level of the CFP in the present investigation as measured on the living proptosed rabbit eye is higher than reported in earlier investigations on the eyes of lower vertebrates Apart from a possible species difference the reasons for this may be found in differing degrees of surface shunting of the CFP and in the possibility that the CFP of the frog eye undergoes a certain amplitude loss in association with enucleation The estimates of the resistive properties of the specimen in the present investigation indicate a change in an intraocular voltage generator rather than in the passive resistive properties of the tissues as the basic phenomenon inducing voltage fluctuations As con cerns the appreciable CFP variations also to be found in mammal eyes under conditions controlled as above the possibility of changing electro chemical conditions at the electrode contact areas especially the posterior (which is the more difficult to control) must be considered

ELECTROOCULOGRAPHY IN HUMAN BEINGS

This field was opened by Miles (1939a b c 1940) who was the first to interest himself systematically in the indirectly recorded CFP in man He laid down the relationship between the potentials as recorded from various electrode placements (nasal temporal bi nasal bi temporal) and found that the potential from one eye spread to the opposite periorbital region The potential range in normal subjects was high (0 3–2 5 mV for a 30 saccade) and for the same subject a range as large as 0 45–1 9 mV was found during one experimental session In repeated examinations of the same subject the first recording always showed a higher potential level which he explained by reference to anxiety during the first session In analogy herewith Arden & Kelsey (1962a) found that during conversation the introduction of an unpleasant subject almost always caused a rise in potential Furthermore Miles demonstrated small EOG changes after application of external pressure to the eye massage of the bulb increase of blood pressure conjunctival instillation of 10% sodium chloride and closure of the palpebral fissure Finally he demonstrated that the smaller potential recorded during dark adaptation differed significantly from the larger potential recorded under light and predicted the importance of this both in basic and clinical research The latter finding will be thoroughly discussed in a subsequent chapter

One point in Miles argument concerning the nature of the recorded voltage changes calls for closer consideration also because it is an implicit or explicit assumption in many later investigations Miles stresses that the use of a vacuum tube voltmeter with an input resistance in the megaohm range guarantees that resistance changes in the measuring object do not influence the voltage readings

Nevertheless as discussed above the eye bulb serves as a voltage divider with respect to the CFP and in the case of indirect recording the circuit in Fig 3 must be supplemented by further shunting resistances corresponding to the tissues interposed between the bulb and the electrodes Theoretically a changing relationship between the resistances in the voltage divider leads to a change in the potential between the skin electrodes The practical importance is difficult to assess in view of the many unknown electrical parameters in the measuring object but in any event Richter & Woodruff (1942) have proved the existence of a sharp borderline in the face between areas of high and low skin resistance There were appreciable interindividual differences as to the location of this border and furthermore it was shown to be mobile in the individual subject and to some extent related to temperature and the waking state In

other words, it would not be justifiable a priori to consider the voltage picked up by periorbital electrodes to be a constant fraction of the CFP

With the exception of the effect of light upon the behaviour of the EOG, comparatively few investigations have considered its normal physiology Aserinsky (1955) and Jacobs et al (1973) noticed a slight increase in the EOG level after sleep whereas Kris (1960) found low values both in the evening and in the morning as compared with recordings taken at noon, and she claimed that a diurnal variation parallel to the body temperature was a likely explanation Davis & Shackel (1960) found no general pattern in the diurnal EOG variation which in their experiments showed a definite individualistic trend Part of these dissimilarities may arise from the fact that different and sometimes small time constants were used in the electronic amplification of the signal thus raising the possibility of an influence from variable eye movement velocity during the day Another part may arise from the less well defined lighting circumstances that were generally used in the above studies

The data of Miles (1939b) suggested a curvilinear relation between age and EOG potential in his female subjects, the highest potentials being recorded in the middle of the three age groups of 10–12 years, 17–19 years and 41–65 years Shackel (1960) found a negative correlation between age and EOG potential in a sample of men of very limited age spread (15–17 years) The correlation disappeared in a re investigation (Shackel & Davis 1960) of the same sample In another investigation of a sample with a greater age span the reverse relation between age and potential level was demonstrated but the difference was not statistically significant (Davis & Shackel 1960)

Fenn et al (1949) studied the effect of anoxia and acapnia upon the EOG and Kolder (1959) noted a dose dependent increase of the EOG after subcutaneous injection of adrenaline Skoog et al (1975) recorded an oscillating CFP after peroral intake of ethyl alcohol It has been shown that the EOG potential is independent of the degree of accomodation (Bornschein & Schubert 1957) Stepanik (1958) could record no significant changes in EOG potential after increasing the intraocular pressure up to 75 mm Hg by means of a suction ring nevertheless both application and removal of the suction cup were followed by large potential changes

Mackensen & Harder (1954) and Alexandridis et al (1975) described a negative correlation between the protrusion of the eye bulb and the EOG potential Furthermore the latter authors found that myopic eyes demonstrated a higher EOG potential level than the contralateral less myopic/emmetropic control eye and that hyperopic eyes analogously had a lower EOG potential level

The relation between the ERG and the EOG has been thoroughly investigated and it is easy to produce opposing changes both by means of light and other stimuli (Muller Limmroth & Lemaitre 1953 Noell 1952 Gliem 1971 Kolder 1974) Nevertheless when examining the c wave of the ERG which is present only with DC amplification a co-variation with the EOG potential can be demonstrated (Nilsson & Skoog 1975)

ILLUMINATION AND THE EOG POTENTIAL

Miles discovery (1940) of the different EOG potential levels during dark and light adaptation was corroborated in 1955 by Aserinsky who further described the occurrence of a short initial decrease of the potential before the light induced rise Aserinsky emphasized the lack of parallelism between these phenomena and the time course of the retinal adaptation to dark and light respectively Next ten Doeschatte & ten Doeschatte (1956 1957) demonstrated that during a sufficiently long dark adaptation period the EOG drop was followed by a rise During light adaptation the variation of the EOG potential was too great to permit any pattern to be recognized Moreover they claimed that a high level of illumination before dark adaptation resulted in a smaller dark minimum value and a longer time span between the beginning of dark adaptation and potential reversal No connexion exists between the potential decrease during dark adaptation and the light sensitivity threshold (François et al 1957 Arden & Kelsey 1962a)

Kris (1958) followed the EOG response to step changes in illumination for up to one hour The EOG potential movements suggested a damped oscillation with a period of about 30 min The rise in potential following a light step was greater when a high intensity stimulus was used Kris also noted a small decrease in potential during the beginning of the light adaptation and a small potential rise at the beginning of the dark adaptation These findings were independently confirmed on a larger scale by Kolder (1959) who further laid down the logarithmic relation between the intensity of the light stimulus and the ensuing EOG potential amplitude and demonstrated a resonance frequency of 2 4/hour corresponding to dark and light periods of 12 5 min each Finally Kolder found a different time course of the oscillations evoked by light and dark steps respectively the latter having a slightly longer period The light induced EOG potential oscillation was later made the subject of several mathematical statistical studies (Homer & Kolder 1966 1967 Homer et al 1967 Benson et al 1967) inspired by the earlier findings of Kolder It was assumed that the EOG oscillation arises from the disturbance of a feedback mechanism with transmission of information between three or four layers Mathematical models containing the solution of three or four linear differential equations

were developed and compared with the experimental findings In the single recordings good concordance could be obtained, but the seven or nine parameters in the equations differed markedly inter as well as intraindividually, and at the present time have no specific anatomical or physiological meanings

The small EOG potential deflections occuring before the main light or dark evoked oscillation were studied in detail by Kolder & Brecher (1966) They were found to represent another resonance frequency of the EOG characterized by dark and light phases of 1 1 min each They interfere with the slow oscillation in the same eye and under suitable experimental conditions they can be elicited from one eye of a test subject the other eye demonstrating a slow oscillation only Their amplitude depends upon the intensity of the light stimulus but contrary to the slow oscillation the potential increases in darkness and decreases during light periods Apart from this, the rapid EOG oscillation has received little attention and its possible clinical implications have not been investigated probably because the recording makes high demands on the alertness and cooperation of the test subject

The investigations of Arden & Kelsey (1962a b) disclosed that quantitative differences existed in the stimulus characteristics of the light induced EOG potential rise and the drop caused by extinction of lights

The relationship demonstrated earlier between the logarithm of the light stimulus and the potential response was confirmed within a range of 20–10 000 Trolands (a unit of retinal illuminance formed by the product of the luminance value (cd/m^2) and the area of the pupillary aperture (mm^2)) Below 20 Trolands the amplitude of the EOG oscillation could not be distinguished from a dark oscillation and above 10,000 no further potential increase was observed the latter result was corroborated by the study of Muller et al (1971) Arden & Kelsey also demonstrated that full development of the light induced potential rise was contingent upon a dark adaptation period not less than 15–20 min before stimulation with light A typical light peak (L) was observed with only 2 min of illumination and the investigation of Gliem (1971) showed that a maximal L for the intensity in question required only 4 min of illumination The duration between the beginning of the stimulus and the occurence of L is fairly unanimously stated to averagely 8–9 min

The study of Arden & Kelsey (1962a b) of the potential drop to a minimum (the dark trough D) during dark adaptation showed that this could also be elicited by a mere reduction of light intensity provided it exceeded 1 69 log units (49 times) According to these authors but in contrast to the findings of ten Doeschatte & ten Doeschatte (1957) the potential falls to a fixed level when the

above mentioned condition is fulfilled irrespective of the intensity of the preadapting light Nevertheless also a later study (Muller et al 1970) questioned this hypothesis These authors recorded two EOG s in a sequence the first with no particular pre adaptation apart from room illumination the second with the 15 min light period of the first as pre adaptation The second EOG presented a significantly smaller D value When the two EOG s with different pre adaptation intensities were recorded on different days this difference disappeared probably because of the increased intraindividual variation which is to be expected after splitting up the experimental procedure

The question must arise whether and to what extent an EOG oscillation is influenced by earlier light or dark induced fluctuations The investigations of Arden & Kelsey (1962a b) suggest that a sufficiently strong step increase in illumination completely re phases the intraocular oscillator On the other hand the investigations of Taumer et al (1974a) indicate that the application of two step illumination changes – in the same or opposite directions and within a certain time span – results in a response which can be interpreted as a summation of two separate oscillations

The investigations of François et al (1965) and Taumer et al (1974a) have made it clear that the rate of illumination change also influences the light induced EOG oscillation The lower limit for a discernible effect appears to be 1 log unit/10 min both for decreasing and increasing stimuli

Every source of light can under suitable conditions evoke a light induced potential rise but Arden & Kelsey (1962b) and Elenius & Lehtonen (1962) established a resemblance between the action spectrum of the light rise and the C I E (Commission Internationale de l Éclairage) standard scotopic luminosity curve Nevertheless the latter authors found a slight discrepancy *for the* longer wave lengths which was corroborated by a later investigation specifically focused upon this problem (Elenius & Karo 1966) This appears to indicate *that* the absorption of light in the rods as well as in the cones forms part of the voltage generating mechanism Infra red radiant energy does not act as a stimulus for EOG oscillations (Anderson & Kolder 1966)

To summarize a sudden increase in illumination causes a rise of the EOG potential the amplitude depending on 1) the length of the previous dark adaptation 2) the intensity and in the case of *monochromatic* light the wave length of the stimulus and 3) the duration of the stimulus With sustained illumination the EOG potential oscillates in a damped manner with a period of about 25 min towards a base line which becomes more or less stable after 60–90 min of constant illumination A reduction in illumination causes a potential drop whose amplitude probably also depends although to a lesser degree than

were developed and compared with the experimental findings In the single recordings good concordance could be obtained, but the seven or nine parameters in the equations differed markedly inter as well as intraindividu ally, and at the present time have no specific anatomical or physiological meanings

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2) In Best s macular dystrophy or vitelliform degeneration an extinguished EOG light rise is characteristic whereas the ERG is subject to no or only minimal changes (Krill et al 1966 François et al 1967) Deutman (1969) discovered that the carrier state could be indicated also by means of EOG which has led to the publication of more family pedigrees (Brink 1974 Cross & Bard 1974)

It is worth emphasizing that the normal ERG mentioned in connexion with the above conditions means a normal clinical ERG (AC amplification) Concerning the close relation between the c wave of the ERG and the EOG (cf Nilsson & Skoog 1975) an ERG recording which includes the c wave might disclose an unbroken parallelism between these two electrophysiological tests

EOG recording procedures

The investigations referred to of the normal and pathological physiology of the EOG are by no means based upon uniform or camparable recording procedures Redlich et al (1945) and Riggs (1954) picked up the periocular potentials rather casually and it was François et al (1955 1956a b 1957) who first realized the need for a standardization and saw the possibility of refining the method by taking into consideration the light and dark induced potential oscillations After a short period in moderate room illumination they registered a base value« later succeeded by a short light adaptation (5 min) followed by 15–20 min of dark adaptation During the period of light adaptation the potential usually dropped and in the ensuing dark adaptation period the drop continued although in some cases preceded by a small rise The drop was expressed in µV as well as in units of the largest recorded potential value The range of variation of all parameters was however high and the authors later (1966) adopted the Arden version of the EOG test (see below)

The information contained particularly in the light induced potential rise was obviously not fully explored in the test of François et al In a pilot study Arden et al (1962) demonstrated that this parameter was much more *sensitive to* retinal pathology than the potential drop during dark adaptation a finding corroborated by Gliem (1971) Consequently Arden & Barrada (1962) introduced a clinical EOG test based on the previous investigations of Arden & Kelsey (1962a b) although modified in a few but probably important points by the use of a smaller dark adaptation period (12 min) and a weaker stimulus than necessary for securing a full light rise They recorded the lowest value during dark adaptation (D) and the largest value during light adaptation (L) Nevertheless even with this procedure the normal variation of the potential figures was enormous From 5–45 µV/*degree of* eye movement in the case of D and from 15–80 µV/degree in the case of L (Arden & Barrada 1962 Fig 1) The authors therefore suggested that a valuable reduction in variation might be achieved by eliminating the influence of the distance between the voltage

for the light induced oscillation, on the intensity difference between light and dark During a period of darkness or reduced illumination, the EOG potential oscillates as described above, but *with a slightly longer period The EOG* exhibits the phenomenon of resonance at two frequencies at least A light or dark induced EOG oscillation probably interferes with oscillations evoked by marked changes of illumination within the previous hour The action spectrum of the light rise suggests that the trigger mechanism comprises the absorption of *light in rods as well* as in cones

THE EOG AS A CLINICAL TOOL

Miles (1939a) already referred to the possible clinical *benefits from the re*cording of EOG potentials and a few years later a study of eye movement and blink potential in 40 patients with various injuries and diseases of the visual apparatus emerged (Redlich et al 1945) No attempt was made to distinguish between EOG and blink potentials and the results were inconclusive In 1954 Riggs reported on a patient with pigmentary degeneration of the retina who demonstrated a very low EOG potential level and since then numerous investigations of the pathophysiology of the EOG have been published Among the more extensive studies are those of François et al (1957) Arden et al (1962) Carr & Siegel (1964) Gliem (1971), Imaizumi (1966) Szmigielski (1968) Kelsey (1968) François & de Rouck (1968), Mackensen et al (1969) and Krill (1970) some of which discuss the value of recording the ERG in conjunction *with the EOG Recent detailed accounts and surveys with references are those* of Deutman (1971) François et al (1974) and Kolder (1974) There is generally a fairly close parallelism between the ERG and EOG responses but for nearly every disease discrepancies have been claimed Since the number of observa*tions contained in* these studies is limited and the results often conflicting they are in most cases best interpreted as demonstrations of sample variation In particular the EOG has been claimed to occupy a position as the most sensitive electrodiagnostic test for diagnostic and prognostic purposes in the following conditions

1) In patients treated with anti malarial drugs in large doses for connective tissue disorders e g lupus erythematosus disseminatus a reduced EOG light *response has been demonstrated* which is sometimes present before any visible foveal changes and sometimes shows amelioration upon cessation of the drug (Arden & Fojas 1962 Elenius & Mantyjarvi 1963 Kolb 1965 Gouras & Gunkel 1963) The reports are by no means unanimous and the observation of Kolb (1965) of subnormal EOG light responses in untreated patients is *probably of importance to this aspect*

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generator and the skin electrodes on the EOG parameter To this end they calculated the percentage increase in potential during light adaptation from the D level ($\frac{L}{D} \times 100$ the Arden ratio) This parameter varied between 191 and 382 with an average of 253 in the normal sample exposed to a stimulus of 3,000 Trolands Naturally enough the average value fell to 223 when a stimulus of less than 350 Trolands was employed The authors suggested a limit of 185 for clearly pathological cases and of 200 for suspicious cases Since then the Arden ratio has gained almost universal acceptance as the most reliable EOG parameter, but only a restricted number of reports on its normal behaviour are available apart from the original paper (Geijer Mannerfelt & Pallin 1968 Reeser et al 1970 van Lith & Balik 1970 Adams 1973, Jones et al 1976) A few other papers have pointed out an apparently conspicuous intraindividual variation of the Arden ratio (Kelsey 1967, van Lith & Balik 1971 Muller & Haase 1970)

Gliem (1971) suggested that a more effective reduction of variation would occur if the light induced potential rise was measured relative to a »base« potential value Consequently he supplemented the Arden test schedule by a 10 min pre adaptation period at the end of which he measured the base value B He evaluated the parameters $\frac{L}{B} \times 100$ $\frac{D}{B} \times 100$ and their difference in samples of normal and pathological eyes The normal average ± S D values were 119 ± 26% for the relative light rise 55 ± 17% for the relative dark drop and 65 ± 22% for their difference $\frac{L-D}{B} \times 100$ In the pathological samples, a reduction in the relative light rise value preceded the similar change in the dark drop

A different procedure was adopted by Pinckers & Thijssen (1971) These authors calculated from a sample of normal values the theoretical light peak value that would arise if an initial value (I) as well as the dark trough were zero (the initial value being recorded after a 15 min pre adaptation period with 100 lx) This value was called the A criterion and the regression equation was

4) $A_{cr} = L - 0\ 61 \times I - 0\ 91 \times D$

A_{cr} is in effect a potential value and therefore theoretically liable to show variation from differing electrode generator distances The authors nevertheless showed that examination of their pathological cases gave more subnormal A values than Arden ratios

Later Thijssen & Pinckers (1970) designed a new EOG test procedure and a new dimensionless expression The illumination period was extended to 40 min which allowed the recording of two light peaks and one or two light troughs The best fitting damped sine wave and its average potential value d were calculated The difference between the first light peak and d was called a and the proposed relative expression $\frac{a}{d}$ A clinical evaluation is in progress The

new expression appears to relate more closely to the A criterion than to the Arden ratio but at the present time no definite statements concerning the clinical value can be given (Thijssen personal communication)

AUTHOR'S INVESTIGATIONS (III–VII)

It may be concluded from the above paragraphs that the EOG in its present modifications is of comparatively little service in the evaluation of the individual clinical case mainly because of the large variability of all parameters hitherto investigated Reasons may be sought in one or more of the following factors

1) *A non optimal testing procedure* If it is assumed that the light induced potential rise is the most sensitive EOG parameter in the presence of retinal pathology the test procedure must secure a complete saturation of the voltage generating mechanism This requires that the prior dark adaptation be of sufficient length (15–20 min as determined empirically by Arden & Kelsey (1962a b) or alternatively be long enough to make allowance for the phenomenon of resonance (Taumer et al 1974a b)) A strong »supramaximal« light stimulus is also a prerequisite failing this the magnitude of the pupillary aperture will gain influence upon the potential response Intensities of ≧ 10 000 Trolands have been found satisfactory (Arden & Kelsey 1962a b) securing independence of the pupillary area (Muller et al 1971 Krogh III)

The angle of eye rotation should be fixed by suitable marks François et al (1957) preferred extreme dextro- and levo-versions but calculated an error of ± 8 5% due to the variability of maximal versions Krogh (III) found that the alternating fixation of two small red bulbs separated by a distance corresponding to 30 degrees was very accurate under varying illumination conditions even when some degrees of visual reduction was present

2) *Too strong filtering of the EOG signal during amplification* As demonstrated above AC amplification of the signal with time constants of up to 5 s introduces a variable amplitude loss as compared with DC amplification Investigations primarily aiming at clinical applications of the EOG (François et al Arden & coworkers Gliem Adams a o) have been performed with AC technique with time constants in the 0 1–2 s range

3) *A possible dependence of the EOG parameters upon other variables of the subject* The few earlier studies concerning the influence of age and of ocular protrusion upon the EOG potential level were discussed in a preceding chapter Concerning the Arden ratio the original investigation (Arden & Barrada

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1962) disclosed a slight decrease with advancing age Gliem (1971) found no correlation with age for his ratio After the beginning of the present investigation, Adams (1973) reported that females showed higher Arden ratio values than men, and Alexandridis et al (1975) claimed an influence on the EOG potential level of the degree of refractive error

The conditions dealt with under (1) and (2) might explain part of the intraindividual variation of the EOG parameters, including the dimensionless expressions, whereas all the factors included under (1), (2) and (3) will add to the *interindividual variation* *Having regard to this the author considered it appropriate to do a normative EOG study with the following aims*

To collect a normal sample (1) of at least 100 eyes showing a representative distribution of age and sex in contrast to earlier literature on the Arden ratio dealing with 5–50 eyes, usually unspecified and sometimes comprised of eyes from subjects with pathological lesions in the other eye Other variables of conceivable interest as concerns the EOG response should be registered and subjected to similar statistical analysis

To study the intra eye variability of the EOG in the present modification Kelsey (1967) and others have claimed a rather wide range of variation in normal subjects to which however the less optimal recording procedure as discussed above may have contributed Repeated EOG recordings from a smaller sample (2) will therefore be analysed

The EOG test schedule and the electronical signal processing should eliminate to the greatest possible extent the sources of variation listed under (1) and (2) In this way possible connexions between EOG and other variables adding to the interindividual variation will stand out more clearly A modified Arden procedure was found to meet this demand in combination with DC amplification Lengthy procedures such as those of Kolder (1959) and Thijssen & Pinckers (1970) were considered unsuitable for clinical purposes

The analysis should embrace EOG potential parameters as well as dimensionless parameters because valuable information might be contained in a parallel analysis and disentanglement of their mutual relations which have not been explored in the earlier EOG literature In addition to the *Arden ratio* the expression devised by Gliem (1971) was included for study in order to assess the value of introducing a base potential level in a parameter retaining the advantage of a dimensionless expression The author considered that the moderate prolongation of the test period by the pre adaptation represented no undue inconvenience to the subject

SELECTION AND DESCRIPTION OF THE SAMPLES

It was decided not to procure the necessary number of test persons by way of the National Register because of the uncontrollable selection induced by this method and because of the foreseeable sorting-out of some responding subjects presenting anomalities of the eye and the visual function Similarly subjects attending an eye clinic could not be included in the study The author therefore made his selection (sample 1) from patients with minor »local« diseases in the departments of orthopedics plastic and maxillo-facial surgery and ENT diseases at Rigshospitalet A gross examination was performed in the respective wards and eyes with present diseases or earlier intraocular affections were excluded together with patients suffering from metabolic circulatory hormonal neurological malignant and connective tissue disorders Only subjects of Caucasian extraction were included and as Rigshospitalet receives patients from the whole of Denmark wide geographical and cultural representation is secured

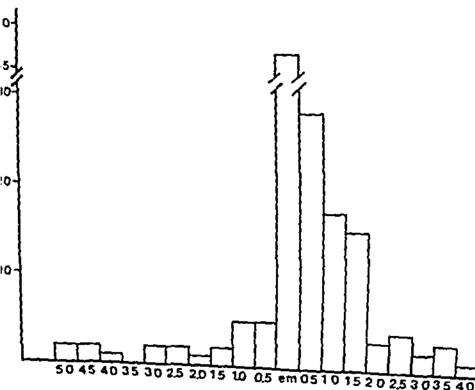


Fig. 4 The non-cycloplegic refractive errors of the 34[illegible] eyes comprising sample 1 Cases of astigmatism are incorporated with their spherical equivalent The figures under the columns represent the upper limits of the 0 5 dpt class intervals

If the first screening was passed, the subject underwent supplementary examination in the eye clinic Criteria for inclusion in the sample were

a) A corrected visual acuity of at least 6/9 and a refractive error not exceeding ± 5 00 dp sph (subjective method without cycloplegia) In cases of astigmatism the limits were ± 6 00 dp equivalent the largest difference allowed for being 2 00 dp The distribution of the refractive errors in this sample (Fig 4) agrees with the results of previous studies (i a Stromberg 1936 Stenstrom 1946) i e only approximately Gaussian with a preponderance of moderate degrees of hypermetropia

b) Normal orbital regions and normal position and motility of the eyes

c) Normal findings – physiologic age variations and slight, myopic peripapillar atrophy included – by slit lamp examination of the anterior segment and by ophthalmoscopy (because of the dilatation of the pupil with Mydriacyl®, this part of the examination was postponed until the EOG had been recorded)

d) An applanatic pressure (Goldmann) of 22 mg Hg or less and normal tangent screen fields (5/1000 white)

Seventy two subjects (142 eyes two eyes being relegated one with an optimal artificial aphakia another with a completely healed scleral perforation) passed the final screening and carried through the following examinations

e) Examination with the Javal Schiotz ophthalmometer (Haag Streit) Seven eyes had no measurable difference in the anterior central corneal curvature whereas the remaining 135 eyes showed a right angled astigmatism The axes of the flattest curvatures were situated in the 0 ± 10 degree range in 69% and in the 90 ± 10 degree range in 19% of the eyes

The radius of the flattest curvature varied between 7 1 and 8 8 mm with a median of 7 8 the corresponding values for the steepest curvature being 6 9–8 7 mm and 7 6 In Stenstrom s investigation (1946) a mean of 7 86 mm was found

f) Measurement of the horizontal diameter of the cornea and the pupil in the Goldmann perimeter with a 45 lx illumination The median of the corneal diameter was 11 5 mm and the range 10 5–12 0 mm which are in agreement with the figures of Johansen (1947) The median pupillary diameter was 3 0 mm with a range of 2 0–7 0 mm It might be argued that the pupil size during the application of the light stimulus in the EOG test is a more relevant measure but this could scarcely be obtained without disturbing the recording of the light

peak However it seems reasonable to assume that good correlation exists between the pupil sizes in the measuring and the testing conditions

g) A measurement of the ocular protrusion (Rodenstock a m Hertel) The median was 16 mm and the range 10–21 mm

h) A measurement of the interpupillary distance (Oculus) The median value was 63 mm and the range 55–69 mm

i) An estimate of the iris pigmentation graded into four classes according to a taxonomic scheme by Tocher (1908) Grade zero (albinos) did not come into consideration Class 1 (slight pigmentation) contained 50 eyes whereas Classes 2 3 and 4 had 35 41 and 16 eyes respectively In one case the two eyes of a subject were placed in different groups the author therefore chose to treat the iris colour as an eye and not subject linked characteristic in the statistical analysis (see below)

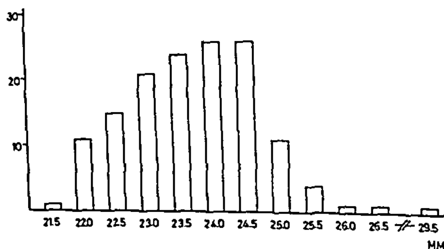


Fig 5 The axial lengths of the 14 eyes comprising sample 1 The figures under the columns represent the lower limits of the 0 5 mm class intervals The columns are separated for typographical reasons

j) Finally and after the EOG recording the axial length of the eye was measured by ultrasonography giving separate figures for the length of the anterior chamber (including the cornea) the lens and the vitreous cavity (Fledelius 1970) but only the total length was used in the statistical analysis The distribution is shown in Fig 5 The median value was 23 9 mm with a range of 21 8–29 5 mm which agrees well with earlier studies (Stenstrom 1946 Jansson 1963)

All examinations were performed in the winter of 1973 between 8 00 and 13 00 hrs On a few occasions more suitable subjects were available than it was possible to examine before they left the hospital, selection was then with a view to the distribution by age and sex

Can this collection of subjects be characterized as a »normal sample«? Two meanings of the word »normal« must be analysed 1) It seems reasonably safe to conclude that the sample does not contain members with eye disorders or general diseases with possible ophthalmological implications 2) A more difficult question is whether the material is representative of a population Reference has been made to the equal representation of each sex and the large age span Moreover in each 20 year age group there is fairly equal representation of the two sexes but if the 10 year age groups are analysed a lack of males in the third decade is found (III, table I) The author decided that the homogeneity of the sample should not be brought into doubt by the inclusion of for example, a number of younger men from the professional group, who might be expected to be of superior understanding and cooperation The distribution of the refractive errors and the axial length have also been alluded to, and as expected they are connected by a significant negative correlation ($r_s = -0\ 41, P < 0\ 001$) There was a statistically significant difference between the axial lengths of the female eyes (median = 23 5 mm) and the male eyes (median = 24 1) (Mann Whitney s test, $P = 0\ 002$) A similar sex difference was noted in the studies of Stenstrom (1946) and Jansson (1963) The female median refractive error in the present material is + 0 50 sph (equivalent) and the corresponding male value 0 00 but no statistical significance could be given to this difference

Earlier Danish investigations of pigmentation of the iris (Eskelund 1938 Jensen 1963) have shown that 61–63% of the examined eyes are fair If the four classes in the present investigation are reduced to two (1+2 and 3+4) the least pigmented eyes account for 60% An examination of the sex ratio in the present material discloses a preponderance of men with fair irides (chi square = 8 47 $P < 0\ 01$)

The remaining variables to be included in the present analysis also vary within normal limits, and in particular no significant differences between female and male values of pupillary diameter and ocular protrusion were found Taking everything into consideration it appears to be justified to draw general conclusions from the present analysis of the normal variability of the EOG including the possible co variation between the EOG and other variables at least for a Danish population Consequently no objection against using the data from the present study as reference values in the clinical EOG evaluation has been disclosed in advance

8 healthy medical students formed sample 2 They underwent the same clinical investigations as the subjects in sample 1

RECORDING PROCEDURE

All recordings took place in a Faraday isolated room with the subject in the supine position Each minute during the test period about 10 saccades between two small red bulbs corresponding to a symmetrical excursion of 30 degrees were performed The induced changes in the periocular electrical field were picked up by lead electrodes placed a few mm from the canthi and amplified and displayed by an ink writer (Siemens Mingograph type M34) The amplifier gain was in the 20–40 μV/mm range and the bandwidth was 0–15 Hz (DC amplification) The deflections lay well within the linearity limit of the writer

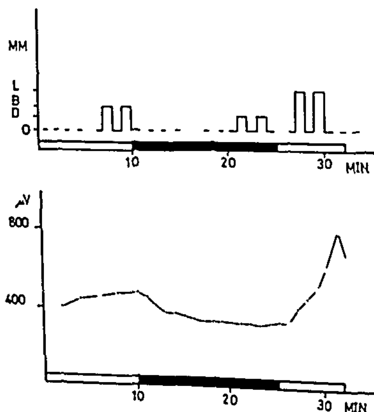


Fig 6 Upper half A standard trace (DC amplification) of equidistant saccades with variations of amplitude according to the illumination conditions Lower half A potential-time curve drawn after transformation of the ink writer deflections into potential values The dark and white bars on the abscissa indicate dark and stimulus periods respectively

The light stimulus was provided by an Osram® 2000 W halogen tube, with a colour temperature of 3200 degrees of Kelvin The light was diffused by an opaque screen mounted in front of the lamp house The intensity as measured at the eye level of the subject was 4000 lx in the central part of the gaze field, decreasing to 2500 lx in the periphery, where the light was reflected from ceiling and walls of a light grey colour

A pre adaptation period of 10 min with the stimulus light initiated the proce dure Just before switching off the light a base value (B) was recorded The dark adaptation period was extended to the moment where the dark troughs (D) were passed with certainty in both eyes Thereafter the stimulus was switched on again until the light peaks (L) were passed

Mean values of the ink writer deflections were calculated for each min of the test The B , D and L values were identified and transformed to μV accord ing to the amplifier gain setting Fig 6 shows a typical recording The period between beginning of dark adaptation and occurrence of the dark trough and the period between dark trough and light peak was measured in min These five parameters together with the variables listed above were transferred to punch cards and filed in the statistical section Rigshospitalet, for statistical and numerical analysis

STATISTICAL AND NUMERICAL ANALYSIS

The distributions of normal EOG parameters in earlier studies showed gross approximation only to the gaussian curve and only a few authors obtained better results from a logarithmic transformation of their data (Arden & Bar rada 1962 Adams 1973) Therefore – and in order to attach as few conditions as possible to the conclusions of the investigation – the present author decided to use *non parametrical statistical methods in the analysis* of sample 1 A third reason for this choice arose from the intention to examine relative EOG parameters (quotients) in addition to the potential and time figures If – for example – two variables each show a gaussian distribution this characteristic will not apply to their quotient (or product) – and vice versa On the other hand more elaborate analyses of variance are not yet feasible with these methods

The hypothesis of no scale shift between two or more sets of data was tested by the following methods Mann Whitney s test for two independent sets of observations Wilcoxon s test in cases of paired observations and Krusk al Wallis test for three or more independent sets of observations The hypothesis of no monotonic relationship in two sets of observations was evaluated by Spearman s rank correlation test expressed as a coefficient (r_s)

The hypothesis of equal dispersion in two distributions with approximately equal central values was estimated by Westenberg s interquartile range test which utilizes Fisher s exact probability test Finally chi square and binomial tests have been applied for appropriate purposes (Siegel 1956 Bradley 1968)

The discussion is based upon a 0 05 limit of significance but all P values at and below this level are stated values below 0 001 being lumped together A two-tailed significance estimate was used Indeed the H statistic in Krusk al Wallis test is assessed by an upper tail region of rejection only but this includes analogous to the chi square test all extreme parameter deviations

Observations from the two eyes of a subject will often show a high degree of accordance and cannot therefore be treated as independent data when related to subject linked variables age sex and interpupillary distance In such cases the average value is used in the statistical analysis

Ratios are commonly used in biometry but their relative inaccuracy and their often unusual distributions must be taken into consideration the latter disad vantage of course being overcome by the non parametrical tests the reader is referred to Sokal & Rohlf (1969) for a detailed discussion of this topic On the other hand the dimensionless EOG parameters are employed with the purpose of obtaining a measure which shows less scattering than the potential figures Obviously quantitative estimates of the relative importance of these opposing characteristics are necessary in each particular case In the present analysis two procedures have been adopted to elucidate this problem

a) The dispersion of the potential and of the dimensionless EOG parameters is represented by the 90–10 percentile range In order to compare parameters with different scale locations or measuring units the range is divided by the appropriate median value

This coefficient of variation is a parallel to the parametric coefficient of variation (Pearson s coefficient $\frac{s}{\bar{x}}$) and shares with it the disadvantage of not being applicable when the central value is close to zero Furthermore the difference between two coefficients cannot be subjected to a significance test

b) An estimate (Δf) of the inaccuracy of the ratios (f) in question given the inaccuracy of the n potential terms is possible using Gauss formula (see Defares et al 1973)

5) $\Delta f = \sqrt{\sum_{1}^{n} (\mathrm{diff}_r)^2}$ where diff_r is the differential of the function f in relation to variable r In order to compare different functions the Δf values are multi plied by $\frac{100}{f}$ and expressed as percentages (P_f)

The data from sample 2 are derived from repeated measurements, which tend to show a Gaussian distribution and are therefore analysed by parametric methods However, the above mentioned problem of distributions of potentials vs quotients necessitates a limitation in the conclusions to mean values whose sampling distribution approximates a normal distribution according to the central limit theorem (see Campbell 1974) The analysis of variance is preceded by Bartlett s test for homogeneity of variance

RESULTS – SAMPLE 1
MEDIAN AND RANGE OF THE EOG PARAMETERS

Potentials (III)

Only 111 B values were recorded because of the limited possibility of compensation of the electrode off set potentials in the recorder The median was 368 µV and the range 148–938 µV (Fig 7)

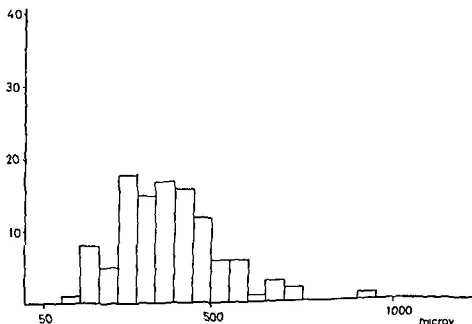


Fig 7 Distribution of the base values of sample 1 class interval = 50 µV

The 31 eyes, in which the base value could not be recorded did not differ in any remarkable way from the total sample There were nearly equal numbers of female and male eyes and of eyes from subjects below and above 50 years of age (binomial distribution $P > 0\ 1$ in both cases)

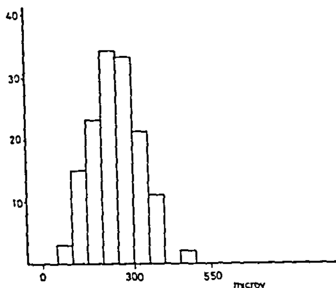


Fig 8 Distribution of the dark troughs of sample 1 class intervals = 50 μV

For the 142 dark troughs the median was 238 μV and the range 71–460 μV (
8) The median value of the light peaks was 565 μV and the range 214–125
(Fig 9) The light induced potential rise of the dark adapted eye (light pe
dark trough) was also calculated The median was 321 μV and the range 71
μV (Fig 10)

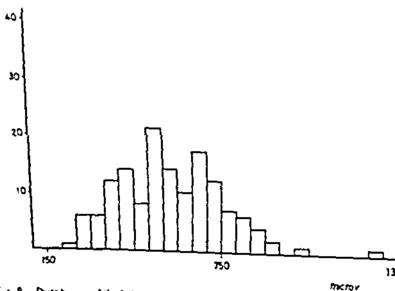


Fig 9 Distribution of the light peaks of sample 1 class interval = 50 μV

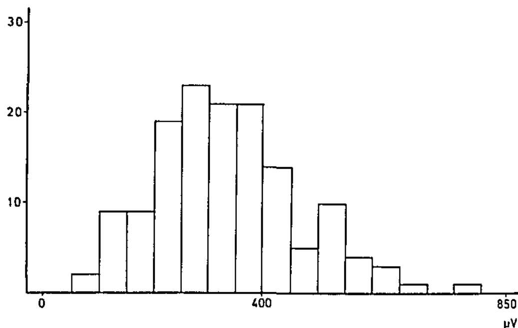


Fig 10 Distribution of the differences between light peak and dark trough of sample 1 class interval = 50 µV

The level of the EOG potentials of the present study is higher than in the investigation of François et al (1957), but smaller than in the studies of Arden & Barrade (1962) and Gliem (1971) The differences are in accordance with the different placement of electrodes and the different time constants applied in the earlier studies DC amplification demands that the electrodes are not placed too close at the canthi

Time factors (III)

The period between the switching off of light and the occurence of the dark trough showed a median of 10 min and a range of 7–15 min (Fig 11) and for the period between the dark trough and the light peak the corresponding figures were 8 min and 5–12 min (Fig 12) These figures agree with those of Arden & Barrada (1962) and Gliem (1971)

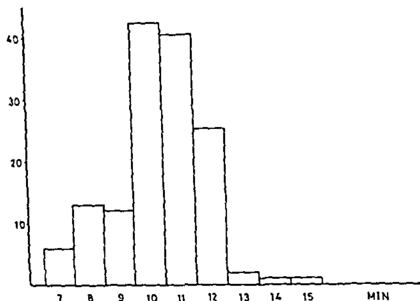
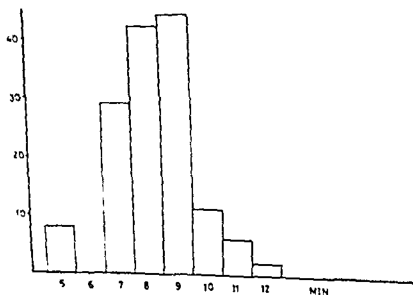


Fig. 11 Distribution of the time spans between the beginning of the dark adaptation and the dark trough of sample 1



F. . 1 Distrib on of the time spa s between the dark trough and the l ght peak of sample 1

Ratios (V)

The median and the range of the Arden ratios were 241 and 148–449 respec-tively (Fig 13) The corresponding Gliem ratio figures were 88 and 34–1(
(Fig 14)

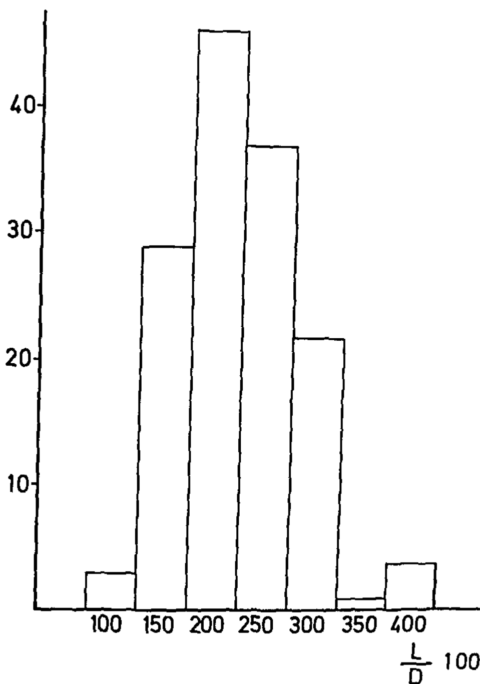


Fig 13 Distribution of the Arden ratios ($\frac{L}{D} \times 100$) of sample 1 The figures under the columns represent the lower limits of the class intervals

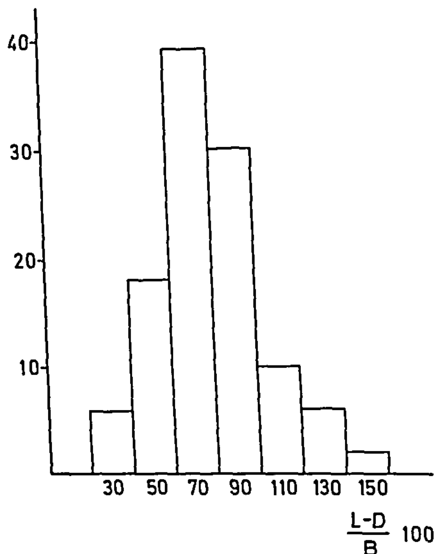


Fig. 14 Distribution of the GI em ratios ($\frac{L-D}{B} \times 100$) of sample I. The figures under the columns represent the lower limits of the class intervals.

The original Arden ratio distribution (Arden & Barrada 1962) is characterized by a contracted range (191–382) and a larger central value (mean value 252, mean value in the present study 247). Arden ratios of 400 and more in the present study is probably contingent upon the use of a longer dark period and a stronger test stimulus. According to ten Doeschatte (1957b) and Taumer *et al.* (1974a, b), a strong pre adaptation stimulus will give rise to a smaller ensuing

Ratios (V)

The median and the range of the Arden ratios were 241 and 148–449 respectively (Fig 13) The corresponding Gliem ratio figures were 88 and 34–167 (Fig 14)

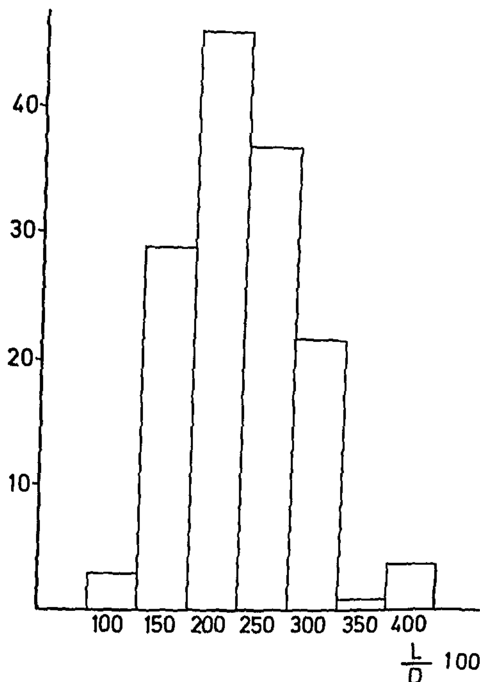


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lated The potential level was positively correlated to the length of time between the beginning of the dark adaptation and the occurence of the dark trough (IV Table VI $P = 0.003$ for L 0.007 for D) No relation between the potential parameters and the interval between the dark trough and the light peak was disclosed by the present investigation

The dimensionless EOG parameters also showed a highly positive correlation (VI Table II $P < 0.001$) They were correlated with the potential parameters D L and L D according to their mathematical connexions (VI Table II $P \leq 0.01$ in all cases) This contrasts with the statement of Arden & Barrada (1962) of no correlation between the EOG potential level represented by D and the Arden ratio which probably reflects a less optimal testing procedure as discussed above However the actual potential level seems to be better approximated by for example $\frac{L+D}{2}$ and between this quantity and the Arden ratio no correlation can be demonstrated in the present study thereby supporting the *conclusion* of Arden & Barrada

The lack of correlation between B and the two ratios would conform with a hypothesis of B as a parameter of restricted variability This can however be discarded by looking at the appropriate frequency diagrams (Fig 7 8 and 9) and comparing the corresponding estimates of dispersion (V) Moreover the scatter diagram of the base values versus the Gliem ratios suggest a parabolic correlation with the largest base values occuring in the central region of the Gliem ratio scale Such a relation cannot be analysed by a test of monotonic co-variation and – if not due to random variation – is difficult to explain

A negative correlation was found between each of the two ratios and the period between the dark trough and the light peak (r_s (Gliem) $= -0.31$ $P < 0.001$ r (Arden) $= -0.23$ and $P = 0.007$) This is a quantitative corroboration and expansion of the statement of Arden & Barrada (1962) that abnormally long peak times are associated with low ratios According to the view of Taumer et al (1974a b) this relation can be explained by a resonance phenomenon with individually varying natural frequencies excited by fixed periods of light and dark adaptation Nevertheless the present recording procedure with individually timed dark periods should afford optimal conditions for resonance At a later stage the analysis will provide evidence which suggests that the negative correlation in question may be secondary to a basic co-variation between the time parameter the ratios and the age of the subject It should however be emphasized that questions of causality *cannot in principle* be answered by a statistical survey no matter how strong the proposed relations may be

dark trough consequently part of the high ratios might be explained by the use of pre adaptation The higher mean value in Arden & Barrada s study is probably explained by its scanty representation of older subjects (see below)

In Gliem s study (1971), the mean value of his ratio is 65 and the range is approximately 20–140 The larger central value (mean = 87) and the up ward shifted range in the present investigation is fully explained by its larger relative light rise (mean value of 143 as opposed to 119 in Gliem s material), the relative dark drops being almost equal Two differences between Gliem s and the present study probably contribute to the different test outcomes First more than half of the eyes in Gliem s normal sample came from patients with eye affections although clinically unilateral Second Gliem s measuring inter vals are 2–3 min (1 min in the present investigation) which means that the light peak in particular may be inaccurately assessed because of the higher rate of voltage change in this part of the test

ACCORDANCE BETWEEN RIGHT EYE AND LEFT EYE VALUES (IV AND VI)

For all the parameters listed above the difference between the distributions of right eye and left eye values were insignificant both in regard to location (Wilcoxon s test) and dispersion (Westenberg s test applied to the potential and relative parameters only the class interval of the time parameters being too large for a reliable estimate) This excludes any systematic right left inequality with regard to electrode setting and stimulus application

Individual side differences were often large (IV and VI Tables I) As exemplifications the medians of the numerical (all differences counted as positive) right left differences are given for the light induced potential rise (51 μV) the Arden ratio (22) and the Gliem quantity (14) When considered in relation to the median values of the total sample the median individual right left difference for the Arden ratio is 9% and for the potential parameter and the Gliem ratio 16% each

MUTUAL CORRELATIONS BETWEEN EOG PARAMETERS (IV AND VI)

All four potential parameters were positively correlated (IV Table II $P < 0.001$ for all combinations) The time parameters were not mutually corre

lated The potential level was positively correlated to the length of time between the beginning of the dark adaptation and the occurence of the dark trough (IV Table VI P = 0 003 for L 0 007 for D) No relation between the potential parameters and the interval between the dark trough and the light peak was disclosed by the present investigation

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ESTIMATES OF PARAMETER DISPERSION AND ACCURACY (V)

The object of this part of the investigation was to compare the distributions of the absolute and dimensionless EOG parameters, since from a theoretical point of view the latter should be relatively inaccurate but are nevertheless claimed *in an EOG context to be superior with respect to dispersion*

The relative dispersion is expressed as a percentile based coefficient of variation (see above) For the potential parameters the following values were obtained B 0 98 D 0 84, L 0 79 and L D 1 1 The values for the Arden and Gliem ratios were 0 65 and 0 82 respectively, the difference being in agreement with the different coefficients for the included potential terms It is seen that only the coefficient for the Arden ratio differs from the coefficients of the potential group as a whole

The average accumulation of errors in the two ratios because of inaccurate assessment of the included potential parameters is estimated by means of Gauss formula (5) The sample medians are used as the potential terms The inaccuracy (d μV) of the potential statements is represented by an estimate of the measuring error of the ink trace Each deflection is recorded with an error of ± 0 1 mm (repeated measurements with slide gauge with 0 05 mm divisions) This figure also represents the maximal – although unlikely – error of the average value of the ten or so deflections recorded every min At the lowest amplifier gain employed (40 μV/mm), the voltage error will be ± 4 μV It is reasonable to assume that this particular error is unaffected by the level of the deflection in other words dB = dD = dL With these figures as exemplifications the formula (5) gives values of 1 8% and 2 0% for the Arden and the Gliem ratios respectively the difference being considered as of no importance The similarly calculated measuring errors of the potential figures are B 1 1% D 1 7% L 0 7% and L D 1 8% Other potential and d μV values will change the individual percentages but not the proportion between them

The conclusion from this part of the study is that although a slightly reduced numerical accuracy (Gauss formula) is demonstrated for the two ratios there is an overall reduction of the scatter (coefficient of variation) when the single potential parameters are substituted by quotients of the same parameters Of the two relative expressions the Arden ratio presents the smallest degree of dispersion

RELATIONS BETWEEN EOG PARAMETERS AND OTHER VARIABLES (IV AND VI)
SEX

Potential parameters (IV)
The levels of B and D were significantly higher in the female half of the sample (P = 0.03 P = 0.005 respectively) A hypothesis of some systematic sex difference in the conducting properties or the electrode setting is not convincing in view of the non significant difference between the female and male light peaks François et al (1957) found no sex related differences in the potential level whereas Hohne (1974) found a systematically higher EOG potential among women in all parts of the voltage time curve It cannot be decided whether the different base value and dark trough levels are caused by retinal or extra retinal voltage contributions

Time parameters (IV)
No significant differences between men and women were found in the present study

Ratios (VI)
The median male Arden ratio of the present sample was 260 in contrast to the female ratio of 235 the difference being statistically significant (P = 0.04) The fact that the proportionally equal difference between male and female Gliem ratios was insignificant may perhaps be ascribed to the smaller number of Gliem ratios The present Arden ratio difference must be interpreted in the light of the significantly higher D level in the female part of the sample

The possible effect of sex upon the Arden ratio has given rise to only a few investigations in the earlier literature Kolder & Hochgesand (1973) found no differences between female and male subjects (N = 37) On the other hand Adams (1973) and Jones et al (1976) found considerably higher Arden ratios in the female half of their samples (N = 170 and 50) There is close correspondence between the female central values of the present study and Adams study whereas the male values in this material exceed those of Adams sample by 40–60 in each 10 year age group Unfortunately Adams provides no information about the potential levels in his sample The slightly different stimulus and recording schedule of the two studies cannot explain this sex related difference and the information in the Scottish investigation do not allow a judgement of possible ethnic or other differences between the samples

Adams (1973) further tried to explain the different mean values in various Arden ratio distributions by referring to the above mentioned sex difference A surplus of women should therefore account for the larger mean values in the

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studies of Arden & Barrada (1962), Geijer Mannerfelt & Pallin (1968) and Reeser et al (1970), and analogously the smaller value in the study of van Lith & Balik (1970) should be explained by a higher proportion of men in their sample This interpretation cannot be supported by the present study

Gliem (1971) did not examine the possible effect of sex upon his ratio

AGE

Potential parameters (IV)

Only the dark troughs showed a conspicuous variation with age Examination of the medians of the seven age groups included in the study (IV, Table IV) suggests a curvilinear trend with the lowest value in the third decade and the most remarkable rise in the direction of the older age groups The overall relation is however a significant positive correlation ($r_s = 0\ 30$, $P = 0\ 01$) The separate female and male coefficients were similar but their significance remains to be proved

The earlier studies of the co variation between EOG parameters and age (Miles 1939b François et al 1957 Shackel 1960, Shackel & Davis 1960 Davis & Shackel 1960) demonstrated no clear or reproducible connexion probably because the samples were small or of restricted age span and examined with less optimal procedures Hohne (1974) found higher EOG potential levels in 17 year old subjects than in 26 year old subjects This corresponds to the figures for the first two decades in the present investigation (IV, Table IV), but the actual difference was not significant (Mann Whitney s test)

In contrast to these studies the senescent period of life is well represented in the present sample The larger dark trough values demonstrated for this group is consequently a new observation, and may be explained either by an increased output from the voltage source(s) concerned or by a change in the conducting properties of the orbital and periorbital tissues

Time parameters (IV)

A positive correlation was found between the age of the subject and the period between the dark trough and the light peak ($r_s = 0\ 29$ $P = 0\ 01$)

Ratios (VI)

Both ratios showed a significant although not strictly monotonic decrease with advancing age (r_s (Arden) $= -0\ 43$ r_s (Gliem) $= -0\ 46$ $P < 0\ 001$ in both cases) The major contribution to this characteristic came from the female part (r_s (Arden) $= -0\ 57$ r_s (Gliem) $= -0\ 61$ $P < 0\ 001$ in both cases) whereas the

male half taken alone demonstrated no significant correlations Arden & Barrada (1962) had found a small negative correlation between the Arden ratio and age which however could not be confirmed in the study of Reeser et al (1970) Neither was such a correlation present in the total sample of Adams (1973) but an analysis of the data from each sex showed that the female ratio declined significantly with age Gliem (1971) found no effect of age upon the Gliem ratio

As usual questions of causality cannot be answered by a statistical survey but as concerns the results of the present study it is reasonable to consider the positive correlation between age and dark trough level as a possible explanation of the negative correlation between age and Arden ratio Nevertheless when each sex is analysed separately a discrepance is noted the age versus dark trough correlation was apparent in the total sample only whereas the age versus Arden ratio correlation predominantly stemmed from the female half of the sample

PUPILLARY DIAMETER

Potential parameters (IV)

A larger pupil was associated with a smaller dark trough level ($r_s = -0\ 24$ $P = 0\ 004$) To explain this it is natural to recall the above disclosed positive correlation between age and dark trough level and the fact that pupil size decreases with age (in the present study r_s for age versus pupil is $-0\ 81$ $P < 0\ 001$) Accordingly a positive correlation between L D and pupil diameter is demonstrated ($r_s = 0\ 20$ $P = 0\ 02$)

Time parameters (IV)

A negative correlation was found between the pupillary diameter and the period between the dark trough and the light peak ($r_s = -0\ 25$ $P = 0\ 01$) which agrees with the joint variation with age of the two parameters

Ratios (VI)

Positive correlations were found between the pupillary diameter and each of the two ratios (r_s (Arden) $= 0\ 35$ r_s (Gliem) $= 0\ 36$ $P < 0\ 001$ in both cases) This relation would be a natural consequence of the use of a submaximal light stimulus The present EOG procedure is however designed and tested against this source of variation (III) Again the relations of the ratios and the pupil size to age fit in with the correlations here indicated

IRIS PIGMENTATION

Potential parameters (IV)

Analyses of variance (Kruskal Wallis test) of the members of the four groups of iris pigmentation showed significant level differences for the dark troughs, the trend being towards an increased level in the darker eyes ($P = 0.008$) Because of the different sex ratios in the four classes, the data from each sex were analysed separately In both sexes Class 3 demonstrated the highest dark trough levels, but the differences were no longer significant According to Gahlot & Hansen (1974) albinotic eyes demonstrate a reduced EOG potential level

Time parameters (IV)

The period between the extinction of the pre adaptation and the occurrence of the dark trough was shorter in fair eyes (Clases 1 and 2 median 10 min in each) than in dark eyes (Classes 3 and 4, median 11 min in each, Kruskal Wallis test $P < 0.001$) This accords with the higher dark trough level in the darker eyes (Class 3 in particular) in combination with the positive correlation between the time parameter in question and the dark trough level

Ratios (VI)

The levels of the two ratios in the four pigmentation groups did not differ significantly (Kruskal Wallis test)

DEGREE OF REFRACTIVE ERROR

Potential parameters (IV)

The light induced potential rise (L D) of the dark adapted eye was associated with the refractive error of the subject in such a way that a larger degree of myopia/smaller degree of hypermetropia were related to larger values of this potential parameter (negative correlation $r_s = -0.20$ $P = 0.02$) This finding is supported by a recent study by Alexandridis et al (1975) of EOG potentials in anisometropic but otherwise normal eyes In the case of a myopic anisometropia the more myopic eye showed the largest potential level and – from their figure – apparently also the largest light induced potential rise In the case of hypermetropic anisometropia the difference between the two eyes was less marked, although in accordance with the presently derived relation

Time parameters (IV)

No connexion between these parameters and the degree of refractive error was found in the present study

Ratios (VI)
The relation between the kind and degree of refractive error and each of the two ratios was in accordance with the above demonstrated correlation between L D and refractive error (r_s (Arden) = -0 19 P = 0 02 r_s (Gliem = -0 21 P = 0 03) In the study of Alexandridis et al (1975) the more hypermetropic and the more myopic eyes both demonstrated smaller Arden ratios than the respective control eyes although the authors stressed that no case of myopic retinal degeneration was present in the sample

AXIAL LENGTH OF THE EYE (IV, VI)

The present study revealed no connexions between this variable and any of the EOG parameters

CORNEAL CURVATURES AND HORIZONTAL DIAMETERS (IV)

These variables being related to the size and form of the globe although less directly than the axial length were included in the study of the potential and time parameters As no relations were disclosed in these respects and as it was difficult to imagine a relation to the dimensionless expressions only they were not further analysed

OCULAR PROTRUSION

Potential parameters (IV)
Only L D was related to the protrusion with a positive correlation (r_s = 0 25 P = 0 002) This is in contrast to the finding (Mackensen & Harder *1954*) of a negative correlation between the protrusion and the EOG potential *recorded* bitemporally and without regard to illumination Alexandridis et al *(1975)* found slightly lower EOG potentials during both dark and light adaptation in protruding emmetropic eyes as compared *with the* contralateral eyes the latter differing at most 1 dp from the fellow eye

Time parameters (IV)
No connexion was found between the degree of ocular protrusion and the two time parameters

Ratios (VI)

A positive correlation existed between the protrusion and each of the two ratios (r_s (Arden) = 0 27 P = 0 001 r_s (Gliem) = 0 27, P = 0 004) Some connexion to the correlations found in the study of the influence of the refractive error may probably be assumed since the more myopic/less hypermetropic eyes generally protrude more (in the present sample, r_s for protrusion versus refractive error = –0 28 P < 0 001)

INTERPUPILLARY DISTANCE (IV AND VI)

In a normal subject each eye generates its own EOG potential field and it appears reasonable to assume a mutual modification Miles (1939a) interpreted the voltage pick up around empty sockets as a spread from the remaining eye and Thijssen & Pinckers (1974) tried to quantify this contralateral effect Theoretically therefore, one might expect a positive correlation to exist between the potential level and the distance between the ocular potential generators The lack of correlation between the interpupillary distance and the potential parameters in the present investigation therefore indicates either that this measure is an inaccurate representation of the voltage generator distance or that the range of the interpupillary distance is too small to allow the detection of a co variation Further no correlation was present or expected between interpupillary distance and the EOG ratios as it must be assumed (Thijssen & Pinckers 1974) that the EOG potentials are affected proportionally by the contralateral effect

DISCUSSION

The recording procedure

When comparing the presently employed stimulus strength and the resulting light induced potential rise with those of earlier studies the importance of a sufficiently strong stimulus is stressed by the presence of higher Arden ratios in this study than in any other normative investigation (V Table I) This expansion of the normal scale width is a necessary consequence of a more complete saturation of the light sensitive EOG voltage generating mechanism although it also increases other things being equal the variability of the EOG In the author s opinion a reduction of the scale width by means of a weak stimulus would give rise to an only apparent increase in accuracy because the pupil size will be introduced as a variable with influence upon the test response

The DC amplification removed the eye movement velocity as a source of variation in the EOG recording (I) In addition it had the great advantage of

allowing a measurement of irregularly performed saccades which were characteristic particularly of older test subjects It is true that the impossibility of recording 31 of the base values must be ascribed to the DC amplification but better means of DC compensation can surely eliminate this group

Potential parameters

It is difficult to draw conclusions from comparisons of the present study with earlier studies because of the sensitivity of potential parameters to electrode placing and amplifier specifications The range of variation in the present study is not less than in most of the earlier investigations (see Arden & Barrada (1962) Table I) which is perhaps explained partly by the optimal stimulus conditions as discussed above and partly by the broader composition of the test sample

Numerous relations between the EOG potentials and the other variables enumerated in this study have been revealed but characteristically the differences are small and the correlations moderate with most coefficients in the ± 0 20 – ± 0 40 range meaning that the particular relation explains only from 4 to 16% of the total variation This indicates either the existence of an unknown variable with influence upon the EOG potentials or that generally the intraindividual precision of the test is low the last explanation being suggested by the often large intraindividual right left differences in otherwise almost similar eyes

For clinical purposes the potential factors are hampered by their dependence upon the technical specifications of the procedure and should be applied only when multiple measurements from a single eye or from a uniform group can be compared with appropriate control measurings

Time parameters

Apparently these parameters demonstrate good individual right left correspondence which probably must be ascribed to the gross measuring unit employed The present investigation has demonstrated that the length of time necessary to reach the light peak increases with age More accurate time statements would require a higher sampling frequency or a direct recording which in both cases would limit the clinical application

Ratios

This investigation has shown a close parallelism between the Arden and the Gliem ratios Gliem (1971) claimed that with the Gliem ratio a smaller degree of dispersion should be obtained than with the Arden ratio The present investigation has demonstrated that the contrary is true in the case of *normal* eyes and the author sees no reason to believe that another relation should be valid in samples of pathological eyes

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Otherwise, the statistical analysis showed that even with relative expressions it is not possible to create a situation of independence from variables such as age, sex, degree of refractive error and ocular protrusion Nevertheless, the amount of variation explained by the correlations to these variables is small, and like the potential parameters, a low intraindividual test precision suggests itself as an explanation Therefore, and having regard to the often contradic tory character of the sporadic statements in the earlier literature regarding these relations, the author does not consider that a splitting up of the normal range with respect thereto is of value

RESULTS AND DISCUSSION – SAMPLE 2

Three EOG s were recorded from each eye of 8 test subjects at weekly intervals The light induced potential rise of the dark adapted eye (L D), the Arden and the Gliem ratio entered into the analysis Graphical representations of the data (Figs 15, 16 and 17) demonstrate large scale widths of all three parameters and also, that the parameters from the two eyes of the same subject do not necessarily show parallel changes during the investigation period, the latter especially characterizing L D

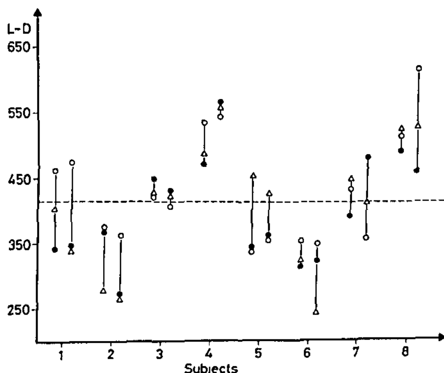


Fig 15 Distribution of the 48 differences between light peak and dark trough of sample 2 The first second and third recordings are represented by open circles filled circles and triangles respectively The dotted line marks the sample mean

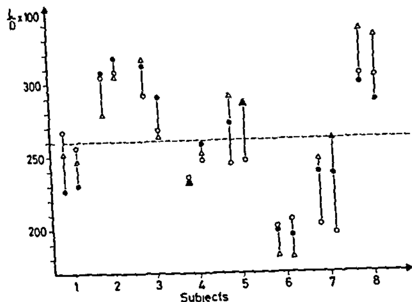


Fig 16 Distribution of the 48 Arden ratios of sample 2 Symbols as in Fig 15

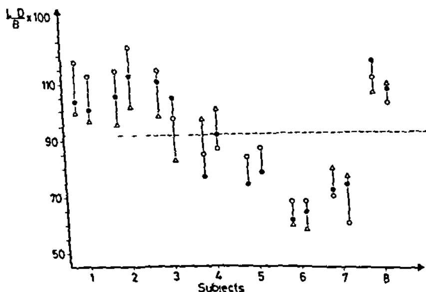


Fig 17 Distribution of the 46 Gliem ratios of sample 2 Symbols as in Fig 15

The null hypothesis of equal variance between the 16 samples was *not rejected* by Bartlett's test The analysis of variance confirmed the visual impression of a large inter-eye variation ($P < 0.001$) The *right left difference* of the mean

within subjects were insignificant (F ratio less than one) Consequently the inter eye variability predominantly arose from the inter subject variability (P < 0 001, VII Table I)

For the clinical EOG recording the precision of the data from the single eye (Figs 15, 16 and 17) is of interest The within eyes variance was calculated in order to state the confidence intervals of the single eye mean value from repeated recordings The 95% confidence intervals of the mean values are calculated by means of the square root, s, of the within eyes variance the sample size and a Student t value of 2 131 (15 degrees of freedom) For L D it is ± 59 μV ± 22 for the Arden ratio and ± 10 for the Gliem ratio The Arden ratio shows the smallest confidence intervals relative to the sample means of 415 μV, 260 and 92 respectively

The investigation thus demonstrates that the EOG is characterized by a limited intra eye precision to such a degree that even mean values from three recordings are subject to considerable uncertainty

Comparisons with earlier studies of the variability of the scotopic b wave of the ERG (Karpe 1945 Spivey & Pearlman 1963) indicate almost the same degrees of intra eye variation of this ERG and the three EOG parameters

CONCLUSIONS – SAMPLE 1 AND 2

The present analysis of both the inter and the intra subject variability indicates that the clinical EOG in the present modification should be considered a qualitative rather than a quantitative test A certain amount of covariation exists between the EOG and other variables of the test subject but their contribution to the total variability is blurred by the presence of an appreciable *intra eye variability which means that the disclosed relations* cannot be used with the aim of refining the reference values

The investigation has also shown that the Arden ratio demonstrates the smallest degree of dispersion both between and within eyes Consequently the original claim of a reduced dispersion of the Gliem ratio as opposed to the Arden ratio has been disproved and it is recalled that the calculation of the former expression requires a slightly extended testing procedure

A suitable threshold value of the Arden ratio based upon the present material and method would be 150 and individual right left differences of up to 90 cannot be considered pathological if both values are greater than 150 The possibilities of ascribing any importance to fluctuations occurring at levels above or below this limit appear to be restricted

FINAL REMARKS

More than twenty years of research have not provided a simple and satisfactory explanation of the puzzling and disturbing variability of CI P and EOG parameters A substantial amount of basic research is still needed in order to determine the relative EOG voltage contributions from the pigment epithelium the retinal layers and other intraocular structures and – not the least – to find means to measure or control the contamination of the pure retinal DC signal with noise from extraretinal potential sources

Meanwhile one may ask how the clinical EOG can be brought to a more useful level than that of a qualitative test characterized by whether or not some threshold value can be passed Considering the limitations regarding the length and complexity of a clinical test procedure the following lines of development appear close at hand

A search of other evaluation procedures Kolder (1959) showed that a stable and illumination independent EOG potential level was obtained after 1-2 hours stay in constant illumination It is possible that this »true« base value can be approximated from inspection of the level and form of a usual 25–30 min recording and incorporated in a hopefully less variable sort of dimensionless expression (Thyssen & Krogh under study)

Also the combination of a potential or dimensionless parameter with the temporal course of the EOG oscillation could be explored In this way for instance the significance of the rate of change of the EOG parameter and its time integrated function during light application can be assessed However this would necessitate a higher sampling frequency – as obtained by direct recording from corneal and skin electrodes with a presumably negligible or constant off set potential difference (Skoog 1975) This technique should also allow a study of the fast EOG oscillations whose clinical aspects are un explored

Finally even if light is the natural stimulus of the CFP other agents might be considered The strongest chemical CFP stimulator known at present – sodium azide (Noell 1952) – cannot be used in humans but characteristic changes of the directly recorded CFP have been induced by ingestion of the less toxic ethyl alcohol (Skoog et al 1975)

Obviously further understanding of these subjects holds great clinical perspectives and fortunately the old and well-established partnership between basic and applied ophthalmic electrophysiology appears to guarantee their continuous exploration

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SUPPLEMENTUM 139

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The Process of Wound Healing of the Avascular Outer Layers of the Retina

Light and Electron Microscopic Studies on Laser Lesions of Monkey Eyes

by

Niels Bulow

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THE PROCESS OF WOUND HEALING OF THE AVASCULAR OUTER LAYERS OF THE RETINA

Light and Electron Microscopic Studies on Laser Lesions of Monkey Eyes

BY

NIELS BÜLOW

Abstract

The process of wound healing of the avascular outer layers of the retina is studied on a series of laser lesions of the monkey *Cercopithecus aethiops*. The extent of the retinal lesions is limited to the pigment epithelium and photoreceptor cells, whereas Bruch's membrane and the vascular inner layers of the retina remain intact.
The retinal lesions are not seen to be invaded by cells from the choroid nor from the retinal vessels. During the first three days after irradiation the pigment epithelial cells in a zone about 5 μm wide around the lesions appear to be changed into bi- or multinucleate cells with the additional nuclei situated in apical cytoplasmic protrusions which extend towards and into the lesions. During the second and third days after irradiation the lesions are invaded by two kinds of cells which both appear to arise through the off-budding of the nucleus-containing apical protrusions of the pigment epithelial cells around the lesions: (a) phagocytic cells which disintegrate the damaged tissue and, as this process is completed 4–5 days after irradiation, show evidence of melanogenesis, and (b) regenerated pigment epithelium which form a single layer of cells along Bruch's membrane but show no evidence of phagocytosis or intracellular disintegration of the damaged tissue. Within the lesions both these kinds of cells show mitotic figures the third day after irradiation.

Key words: retina – pigment epithelium – photoreceptors – laser lesions – wound healing – phagocytic cells – melanogenesis

animal 4 32 40 and 48 h in the second animal 48 56 64 and 72 h in the third animal and 3 4 6 9 13 18 25 and 35 days in the fourth animal

The lesions were produced with a normal mode Ruby Laser providing radiation at 6943 Å with a pulse length of 0.5 ms and a beam divergence of 0.5 corresponding to a retinal image about 0.2 mm in diameter Each lesion was produced by one pulse with a total energy output about 5 mJ corresponding to an energy density of 16 J/cm² in 0.5 ms, and a power density of 32 kW/cm² when absorption in the ocular media is not taken into account

The lesions were placed around the fovea one in each quadrant at a distance from the fovea corresponding to 2/3 of the distance between the fovea and the optic nervehead Ophthalmoscopically all lesions immediately appeared as a grey patch without gas bubble or haemorrhage In order to facilitate the later isolation of the lesions their positions were marked on a drawing of the particular retinal vasculature

Before each exposure the animals were anaesthesized by im injection of Ketamin hydrochloride 10 mg/kg and the pupil was dilated by application of a drop of Cyclopentolate hydrochloride 0.5% and a drop of Metaoxedrin 10%

The eyes were fixed for 1 h by a combination of cardiovascular perfusion and intraocular instillation of glutaraldehyde 2.5% in 0.1 M cacodylate buffer pH 7.4 according to a method previously described (Bulow 1975)

The lesions were isolated in the buffer under a dissecting microscope so that each lesion was contained in a chorioretinal specimen measuring about 1 1.5 mm in the retinal plane The specimens were postfixed for 2 h in osmium tetraoxide 1% in 0.1 M cacodylate buffer pH 7.4 dehydrated and embedded in epon

For light microscopy 1 μm sections were cut perpendicular to the retinal plane and stained with toluidine blue Beginning with the section in which the Laser lesion first appeared serial sections were made half way through the lesion Selected areas in the remaining halfpart of the lesions were cut need at 500 600 Å for electron microscopy and the sections were contrasted with uranyl acetate and lead citrate

Results

Light microscopy of the 10 min old lesion

The lesion involved the choroid the retinal pigment epithelium and the photoreceptor cells (Fig 1)

The choroid was damaged within a poorly *defined space* where some melanocytes appeared to be disrupted The choriocapillaris was *corresponding* to the extent of the lesion in the pigment epithelium occluded by inflam

Introduction

The retinal pigment epithelium is considered to play an important role in the process of wound healing of the avascular outer layers of the retina Recent investigations suggest three related possibilities (1) the phagocytic activity of the pigment epithelium (Feeney 1973 Hollyfield & Ward 1974a b c Leuenberger & Novikoff 1975 Reich d Almeida & Hockley 1975a b) (2) the proliferation of pigment epithelial cells (Marshall & Mellerio 1970 Marshall et al 1971 Ishikawa et al 1973 Wallow & Tso 1973 Ishikawa 1974 Ino mata 1975 Machemer & Laqua 1975) and (3) the origin of migrating pha gocytic cells from the pigment epithelium (Gloor 1969 Lerche 1972 Ma chemer & Laqua 1975)

However none of the three possibilities are sufficiently clarified The pro cesses by which damaged tissue may be removed by the pigment epithelium the processes by which pigment epithelial cells may proliferate after retinal lesions and the processes by which migrating phagocytic cells may arise from the pigment epithelium have not been followed

As an approach to the investigation of these processes morphological studies have been made on the normal retina and on a series of retinal Laser lesions of the monkey *Cercopithecus aethiops* In the normal retina the rela tions between the photoreceptors and the pigment epithelium and the different types of inclusions in the pigment epithelial cells have been described and discussed (Bulow 1975) The present paper provides a survey of the studies on Laser lesions with special emphasis on the process of wound healing

The lesions were produced by Laser irradiation because it had been shown by other authors (Line & Geeraets 1965) that the extent of Laser lesions may be limited to the pigment epithelium and photoreceptor cells whereas Bruch s membrane and the vascular inner layers of the retina may remain intact In the series of Laser lesions studied short time intervals were chosen during the first three days after irradiation as preliminary studies on cell cultures sug gested that proliferation of the pigment epithelial cells might occur during that period

Material and Methods

In the monkey *Cercopithecus aethiops* (Brunnich) a series of 20 perifoveal Laser lesions were produced four in each eye In three animals the lesions were produced in the right eye at time intervals of eight hours whereas the left eyes were used as normal material (Bulow 1975) In a fourth animal the lesions were produced in both eyes at different time intervals When they were fixed the age of the lesions was 10 min 8 16 and 24 h in the first

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matory cells which appeared undamaged Bruch s membrane was intact and was not seen to be penetrated by any cell

The retinal pigment epithelium was damaged within a well defined space In planes parallel to the retina the lesion was nearly circular about 200 μm in diameter judged by the halfpart of the lesion examined in serial sections In the sections perpendicular to the retina the borders of the lesion in the pigment epithelium con erged towards Bruch s membrane (Fig 2) so that the diameter of the les on was about 30 μm larger in the apical part of the pigment epithelium than in the basal part of the cell layer

In the lesion in the pigment epithelium the cells appeared to be disrupted and separated from Bruch s membrane (Figs 1 2) Their cytoplasm showed increased stainability with toluidine blue The nuclei were irregular with clumped chromatin and showed varying degrees of increased stainability The melanin granules were dispersed in the apical part of the cells and be tween the tips of the outer segments of the photoreceptors o that the usual relations between the pigment epithelium and the photoreceptors were dis arranged

In the pigment epithelium surrounding the lesion the cells forming the borders of the lesion appeared to be deformed (Figs 1 2) The surfaces by which the cells delimited the lesion were inclined to the retinal plane their apical parts being inclined away from the lesion The nuclei of the cells forming the borders of the lesion were also deformed being flattened in the parts facing the lesion and Bruch s m mbrane Otherwise the pigment epithe lium surrounding the lesion appeared undamaged

In the neural retina the photoreceptor cells histologically related to the lesion in the pigment epithelium were damaged The tips of their outer seg ments were distorted In addition to this most of the rod and a few of the cone cells related to the lesion in the pigment epithelium were damaged throughout their whole lenght (Fig 1 6) Their cytoplasm was vacuolated and in mo t cases showed an increased stainability which in the serial sections could be foll wed from their inner segments to the synapses in the outer plexiform layer Their nuclei showed varying degrees of pyknosis clumped chromatin and increased stainability However most of the cone and a few of the rod cells histologically related to the lesion in the pigment epithelium showed no other signs of damage than the distortion of the tips of their outer segments The intercellular substance between the outer segments of the photoreceptors h wed no other signs of damage than the disarrangement adjacent to the damaged pigment epithelium

The photoreceptor cells histologically related to the pigment epithelium surrounding the lesion and the inner layers of the retina from the synapses in the outer plexiform layer to the inner limiting membrane appeared undamaged No inflammatory cells were seen in the retina

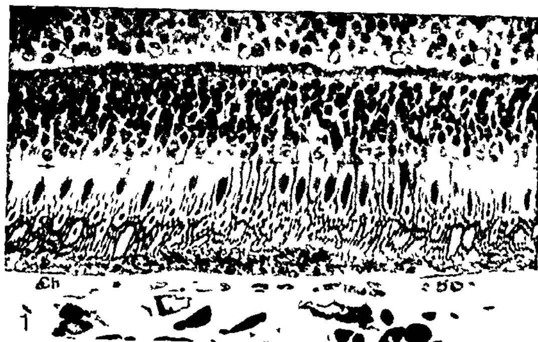




Fig 1 Section perpendicular to the retinal plane showing the 10 min old lesion *Open arrow* retinal capillary in the inner nuclear layer *R* rod nuclei *C* cone nuclei *Short arrow* outer limiting membrane *I* inner segments of the photoreceptors *O* outer segments of the photoreceptors *P* pigment epithelium *Ch* choriocapillaris Compare with the normal retina (Bulow 1975)
× 375

Fig 2 The border of the lesion in the pigment epithelium from the section shown in Fig 1 *Note the inclination of the surface (short arrow) by which the surrounding* pigment epithelium (*P*) delimit the lesion *Long arrow* Bruch's membrane
× 1500

Electron microscopy of the 10 min old lesion

In the choroidal part of the lesion the melanocytes were disrupted and their melanin granules were dispersed in the intercellular substance. The inflammatory cells which occluded the choriocapillaris showed no signs of damage. Bruch's membrane appeared as usual (Fig. 4).

In the lesion in the pigment epithelium the cells were disrupted (Figs. 4, 5). In the major central part of the lesion their cytoplasm and nuclear chromatin was condensed and clumped. However, in a part of the cells situated at the periphery of the lesion the cytoplasm was not condensed, but the endoplasmic reticulum appeared to be disrupted and distended (Fig. 3). The melanin *granules and other inclusions* of the cells were *dispersed in the remnants of* the cells and in the intercellular substance between the tips of the outer segments of the photoreceptors. The structure of *the individual melanin granules* appeared unchanged.

In the pigment epithelium surrounding the lesion the cells forming the borders of the lesion were intact but somewhat deformed (Fig. 3). The surfaces by which the cells delimited the lesion were seen to be the inclined lateral surface membranes of the cells. The deformation of the cells and the inclination of their lateral surface membranes were most pronounced at the borders of the lesion and gradually disappeared about 50 μm from the lesion. In the deformed cells there was some deformation and displacement of the *cellular components*, but otherwise they appeared undamaged.

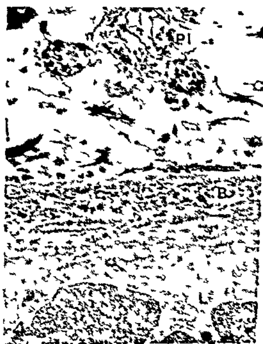
In the lesion in the neural retina most of the rod and a few of the cone cells showed nuclear pyknosis and a homogenization of the cytoplasm extending from the inner segments to the presynaptic membranes in the outer plexiform layer. The nuclei and the *cytoplasm of the other photoreceptor* cells histologically related to the lesion in the pigment epithelium showed no signs

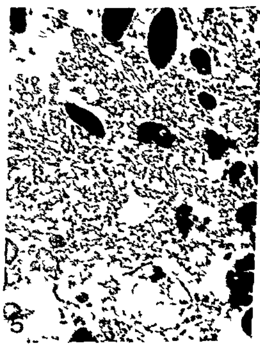
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Fig. 3. Electron micrograph from the border of the 10 min old lesion in the pigment epithelium. *Ps* deformed but intact pigment epithelial cell which contains a deformed nucleus (N). *Pl* disrupted pigment epithelial cell with distended endoplasmic reticulum. *J* part of the lateral junctional complex. Note that the lesion is delimited by the inclined lateral surface membrane of the intact cell. *B* Bruch's *membrane*.
× 300

Fig. 4. *Ll* basal portion of the disrupted pigment epithelium *in the central* part of the 10 min old lesion. *B* Bruch's membrane. *L* undamaged inflammatory cell in the choriocapillaris.
× 300

Fig. 5. The apical portion of the disrupted pigment epithelium in the central part of the 10 min old lesion. Note the condensation *and clumping* of the cytoplasm.
× 300


Pl
B


5

Electron microscopy of the 10 min old lesion

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In the lesion in the neural retina most of the rod and a few of the cone cells showed nuclear pyknosis and a homogenization of the cytoplasm extending from the inner segments to the presynaptic membranes in the outer plexiform layer The nuclei and the cytoplasm of the other photoreceptor cells histologically related to the lesion in the pigment epithelium showed no signs

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Fig 3 Electron micrograph from the border of the 10 min old lesion in the pigment epithelium *Pi* deformed but intact pigment epithelial cell which contains a deformed nucleus (N) *Pl* disrupted pigment epithelial cell with distended endoplasmic reticulum *J* part of the lateral *junctional complex* Note that the lesion is delimited by the inclined lateral surface membrane of the intact cell *B* Bruch s membrane ×6500

Fig 4 *Pl* basal portion of the disrupted pigment epithelium in the central part of the 10 min old lesion *B* Bruch s membrane *L* undamaged inflammatory cell in the choriocapillaris ×6500

Fig 5 The *apical portion* of the disrupted pigment epithelium in the central part of the 10 min old lesion Note the condensation *and clumping of* the cytoplasm ×6500

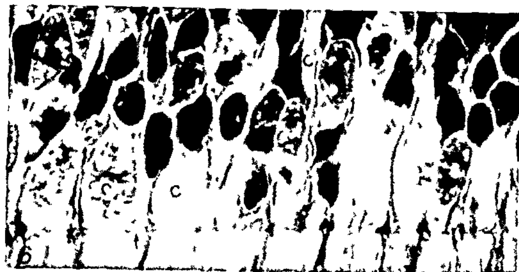




Fig 6 Part of the outer nuclear layer and the inner segments of the photoreceptors in the central part of the 10 min old lesion The damaged photoreceptor *cells* show nuclear pyknosis and dark cytoplasm Note that the nuclei and the cytoplasm of some cones (*C*) appear undamaged *Arrow* Muller fibre between undamaged cone and damaged rod at the level of the outer limiting membrane
× 1500

Fig 7 Undamaged Muller fibre (*M*) between undamaged cone (*C*) and damaged rod (*R*) at the level of the outer limiting membrane From the central part of the 10 min old lesion
× 57000

of damage The cytoplasmic extensions of the Muller cells also appeared undamaged even when they were situated adjacent to damaged photoreceptor cells (Fig 7) The intercellular substance between the outer segments of the photoreceptors showed no other signs of damage than the disarrangement adjacent to the disrupted pigment epithelium The inner layers of the retina from the postsynaptic membranes in the outer plexiform layer showed no signs of damage

Comparison between the various lesions (Light and electron microscopy)

1 *General observations* In the retina the extent of the lesions was in all specimens limited to the pigment epithelium and photoreceptor cells

In all lesions Bruch s membrane was intact and the retinal part of the lesions was not in any case invaded by cells from the choroid nor from the retinal vessels judged by the observations on serial sections

Lesions of different age showed a number of differences which appeared and will be described below as changes which progressed with increased age of the lesions

Lesions of equal age in different eyes and animals appeared similar to each other

2 *Changes during the first day after irradiation* – (Comparison between the 10 min 8 h 16 h and 24 h old lesions)

Retinal oedema was found in the 8 to 24 h old lesions but inflammatory cells were not present in the retina The oedema was most pronounced in the 8 h old lesion (Fig 8) The extent of the oedema was delimited at the plane of the synapses in the outer plexiform layer but at the level of the outer segments of the photoreceptors the oedema reached about 50 μm outside the lesion 16 h efter irradiation the degree and extent of the oedema was decreased and 24 h after irradiation the oedema was discernible only as a swelling of the intercellular substance at the level of the outer segments of the photoreceptors (Fig 11)

The pigment epithelial cells in a zone about 50 μm wide around the lesions showed a number of changes The deformation of the nuclei of the cells forming the borders of the 10 min old lesion (Fig 2) was not found around the older lesions (Figs 8 11) Cells containing a nucleus with a constriction perpendicular to the retinal plane or two *nuclei situated in the usual basal* position appeared in increased numbers in this zone around the lesions (Figs 9 10) Mitotic figures were not seen The cytoplasm of the cells contained increased amounts of vacuoles in the endoplasmic reticulum increased *amounts* of polysomes and increased amounts of small granular lamellar *inclusions The* volume of the cytoplasm of the cells forming the borders of the lesions appeared to be increased 16 to 24 h after irradiation





Fig 6 Part of the outer nuclear layer and the inner segments of the photoreceptors in the central part of the 10 min old lesion The damaged photoreceptor cells show nuclear pyknosis and dark cytoplasm Note that the nuclei and the cytoplasm of some cones (*C*) appear undamaged *Arrow* Muller fibre between undamaged cone and damaged rod at the level of the outer limiting membrane
× 1500

Fig 7 Undamaged Muller fibre (*M*) between undamaged cone (*C*) and damaged rod (*R*) at the level of the outer limiting membrane From the central part of the 10 min old lesion
× 5,000

From the pigment epithelium around the 24 h old lesion a number of cytoplasmic protrusions extended into the retinal part of the lesion. The base of the protrusions was the apical cytoplasm of the pigment epithelial cells forming the borders of the lesion (Fig. 1°). The protrusions extended into the lesion apically to the inclined lateral surface membranes by which the cells delimited the lesion. They continued into the lesion apically to the disrupted pigment epithelium and ramified in the intercellular substance between the damaged outer segments of the photoreceptors. The cytoplasm of the protrusions contained an elaborate system of agranular endoplasmic reticulum, a number of polysomes, small profiles of granular endoplasmic reticulum, Golgi complexes, mitochondria and small granular lamellar inclusions. However the protrusions contained only a few melanin granules. In some cases the ramifications of the protrusions were moulded around or contained structures which appeared as condensed and deformed pieces of the damaged outer segments of the photoreceptors (Fig. 14).

The damaged tissue in the retinal part of the 8 to 24 h old lesions showed moderate changes compared with the 10 min old lesion. In the disrupted pigment epithelium most of the nuclei were discernible only as a vacuolated meshy material (Fig. 11). Some of the outer segments of the photoreceptors were distended and deformed (Fig. 11) showing irregular expanded inter and intra disc spaces (Fig. 13). In the 24 h old lesion some of the outer segments of the photoreceptors appeared as a number of variously sized clumps (Fig. 11) which by electron microscopy appeared as condensed and deformed pieces of the outer segments contained in the cytoplasmic protrusions of the

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Fig. 8. Part of the 8 h old lesion is shown in the left side of the figure. *Arrow*: the inclined surface by which the surrounding pigment epithelium (to the right) delimit the lesion (to the left). Note the shape of the nucleus in the pigment epithelial cell forming the border of the lesion.
× 600

Fig. 9. The border of the 8 h old lesion in the pigment epithelium. The section was taken 4 µm from that shown in Fig. 8. *Arrow*: the inclined surface by which the surrounding pigment epithelium (*P*) delimit the lesion. Note that the pigment epithelial cell forming the border of the lesion appears to contain two nuclei or one nucleus with a constriction perpendicular to the retinal plane.
1,500

Fig. 10. From the pigment epithelium 5–10 µm outside the borders of the 8 h old lesion. *Note that the cell contains two nuclei* (N) or one nucleus with a *constriction* perpendicular to the retinal plane. *P*: polysomes; *V*: vacuoles in the endoplasmic reticulum.
× 400

8





8





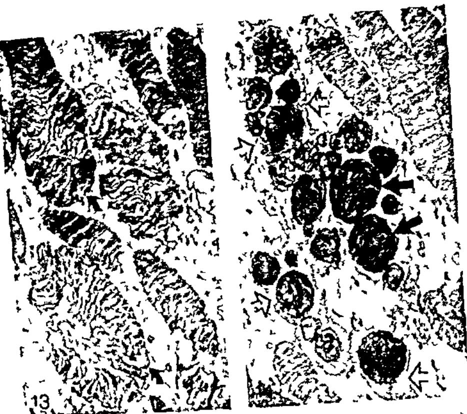


Fig 13 Di ten led parts of the outer segments of the photoreceptors (*curved arrows*) in the 24 h old lesion

6 00

Fig 14 Struct res which appear as condensed and deformed pieces of the outer seg n ents of the photor ceptors (*solid arrows*) in the 24 h old lesion *Open arrows* point t the plasma membrane of the cytoplasmic protrusions which invade the lesion from the apical part of the p gment epithelium immediately outside the lesion

6 00

Fig 11 Part f the 4 h old lesion is shown in the right s de of the figure Note that the nuclei and the cyt plasm of some cones (*C*) appear undamaged Some of the outer segm nts of the photoreceptors are distended (*curved arrow*) Other photoreceptor o ter egm nts appear as variously sized clumps within irregular slender envelopes (*straight arrow*) *Pl* d s upted pigment epithelium with vacuolated nuclei *Ps* pigment ep th lium surro nding the lesion. *Ch* choriocapillaris

(00)

Fig 1 From the bo ler of the 4 h old les on in the p gment epithelium The retinal les n n the upper left corner f the figure is invaded by a cytoplasmic protrusion (*open arrows*) from the ap al part of the pigment epithelial cell (*Ps*) forming the b r ler f the l sion. *J* part of the lateral junctional complex *Solid arrow* the inclined l teral surface m mbrane l li ting the lesion *B* Bruch s membrane

(300)

Ps
Pl
11
Ch
Ps
B
12





Fig 13 Distended parts of the outer segments of the photoreceptors (*curved arrows*) in the 24 h old lesion
× 480

Fig 14 Structures which appear as condensed and deformed pieces of the outer segments of the photoreceptors (*solid arrows*) in the 24 h old lesion *Open arrows* point to the plasma membrane of the cytoplasmic protrusions which invade the lesion from the apical part of the pigment epithelium immediately outside the lesion
6300

Fig 11 Part of the 4 h old l si n is shown in the right s de of the figure Note that the nuclei and the cyt plasm f some cones (*C*) appear undamaged Some of the outer segments of the photoreceptors are distended (*c rved arrow*) Other photoreceptor outer segments appear as variously sized clumps within irregular slender envelopes (*straight arrow*) *PI* disrupted p gm ent epithelium with vacuolated nuclei *Ps* p gment p th lium surrounding the les on *Ch* choriocapillaris
600

Fig 1 From the border f the 4 h old lesion in the pigment epithelium The retinal l si n th upp r left corn of the figure is invaded by a cytoplasmic protrusion (open a) fr m the ap cal part of the p gment ep thelial cell (*Ps*) forming the bo d r f the les n *J* part of the lateral juncti nal complex *Solid arr w* the inclined late al urfa e membrane deli iting the lesi n *B* Bruch s membrane
1 500

pigment epithelial cells surrounding the lesion (Fig 14) The inner segments and the nuclei of the damaged photoreceptor cells showed varying degrees of swelling vacuolation and clumping (Fig 11)

The choroidal part of the 8 to 24 h old lesions was oedematous and invaded by inflammatory cells similar to those which occluded the choriocapillaris The inflammatory cells appeared to be moulded around and contain the melanin granules and other remnants of the damaged choroidal tissue

3 *Changes during the second day after irradiation* (Comparison between the 24 h 32 h 40 h and 48 h old lesions)

The pigment epithelial cells in a zone about 75 μm wide around the lesions appeared to be changed into bi or multinucleate cells with the additional nuclei situated in apical cytoplasmic protrusions which extended towards and into the retinal lesions Mitotic figures were not seen In this zone around the lesions the number of cells containing a lobed nucleus or several nuclei was increased Often one of the nuclei or part of a lobed nucleus was situated in an unusual apical position in the cell at or apically to the level of the lateral junctional complexes (Figs 15–17 19–21) The cytoplasm of the cells contained increased amounts of polysomes profiles of granular endoplasmic reticulum and mitochondria but decreased amounts of small granular lamellar inclusions The cells showed increased volume of their cytoplasm which

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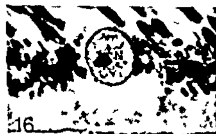
Fig 15 The pigment epithelium about 50 μm outside the borders of the 32 h old lesion Note that the cells appear to contain more than one nucleus (N) or a lobed nucleus *Arrow* Bruch s membrane
× 1500

Fig 16 The pigment epithelium about 50 μm outside the borders of the 32 h old lesion V nucleus situated in an unusual apical position in the cell *J* lateral junctional complex
× 1500

Fig 17 The pigment epithelium about 50 μm outside the borders of the 32 h old lesion One of the nuclei or part of a lobed nucleus (V) is situated between the tips of the outer segments of the photoreceptors apically to the lateral junctional complex (*J*) and the melanin granules
× 1500

Fig 18 Electron micrograph from the pigment epithelium about 0 μm outside the borders of the 32 h old lesion V nuclei *Open arrows* point to the plasma membrane of a phagocytic cell or a nucleus containing apical cytoplasmic protrusion of the pigment epithelium *Solid arrow* structures which appear as the remnants of the damaged tissue
× 4200


N
15


N
16


N
17

extended as apical protrusions towards and into the lesions (Fig 29) Some of these apical cytoplasmic protrusions contained a nucleus or part of a lobed nucleus (Figs 18 22 30–31)

The nucleus containing apical cytoplasmic protrusions of the pigment epithelial cells around the lesions first appeared 32 h after irradiation Their number and volume increased during the second day after irradiation From the apical part of the pigment epithelial cells they extended towards the lesion where they continued apically to the disrupted pigment epithelium and ramified in the intercellular substance between the damaged outer segments of the photoreceptors (Fig 29) The nuclei of the protrusions were variously sized and shaped but otherwise appeared as pigment epithelium nuclei (Figs 18 22 30–31) The cytoplasm of the protrusions contained an elaborate system of agranular endoplasmic reticulum great amounts of polysomes many profiles of granular endoplasmic reticulum Golgi complexes mitochondria and small granular lamellar inclusions However the protrusions contained only a few melanin granules The amount of small granular lamellar inclusions decreased during the second day after irradiation The part of the protrusions situated outside the lesions appeared to push away the outer segments of the photoreceptors However the part of the protrusions situated within the lesions were moulded around or contained great amounts of structures which appeared as condensed and deformed pieces of the damaged outer segments of the photoreceptors

The retinal part of the lesions appeared to be invaded by a kind of cells which were classified as phagocytic This kind of cells first appeared singly 32 h after irradiation just apical to the pigment epithelium immediately surrounding the lesion (Fig 18) They were very similar to the nucleus containing apical cytoplasmic protrusions of the pigment epithelial cells and could be distinguished from them only by outlining the plasma membranes of the cells in serial sections

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Figs 19 20 & 21 Serial 1 *um* sections from the border of the 40 h old lesion in the pigment epithelium *Arrow* the inclined surface by which the surrounding pigment epithelium (*P*) delimit the lesion *N* nuclei Note that festoon like series of irregular nuclei or parts of lobed nuclei extend from the apical part of the pigment epithalial cell forming the border of the lesion into the retinal part of the lesion
× 1500

Fig 22 Electron micrograph from the border of the 40 h old lesion in the pigment epithelium *I* pigment epithelial cell forming the border of the lesion *Solid arrows* the inclined lateral surface membrane delimiting the lesion *Open arrow* points to the plasma membrane of a cytoplasmic protrusion which containing a nucleus or part of a lobed nucleus (*N*) invade the retinal lesion from the apical part of the pigment epithelial cell
× 4200







22

extended as apical protrusions towards and into the lesions (Fig 29) Some of these apical cytoplasmic protrusions contained a nucleus or part of a lobed nucleus (Figs 18 22 30–31)

The nucleus containing apical cytoplasmic protrusions of the pigment epithelial cells around the lesions first appeared 32 h after irradiation Their number and volume increased during the second day after irradiation From the apical part of the pigment epithelial cells they extended towards the lesion where they continued apically to the disrupted pigment epithelium and ramified in the intercellular substance between the damaged outer segments of the photoreceptors (Fig 29) The nuclei of the protrusions were variously sized and shaped but otherwise appeared as pigment epithelium nuclei (Figs 18 22 30–31) The cytoplasm of the protrusions contained an elaborate system of agranular endoplasmic reticulum great amounts of polysomes many profiles of granular endoplasmic reticulum Golgi complexes mitochondria and small granular lamellar inclusions However the protrusions contained only a few melanin granules The amount of small granular lamellar inclusions decreased during the second day after irradiation The part of the protrusions situated outside the lesions appeared to push away the outer segments of the photoreceptors However the part of the protrusions situated within the lesions were moulded around or contained great amounts of structures which appeared as condensed and deformed pieces of the damaged outer segments of the photoreceptors

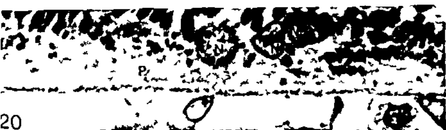
The retinal part of the lesions appeared to be invaded by a kind of cells which were classified as phagocytic This kind of cells first appeared singly 32 h after irradiation just apical to the pigment epithelium immediately surrounding the lesion (Fig 18) They were very similar to the nucleus containing apical cytoplasmic protrusions of the pigment epithelial cells and could be distinguished from them only by outlining the plasma membranes of the cells in serial sections

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Figs 19 20 & 21 Serial 1 μm sections from the border of the 40 h old lesion in the pigment epithelium *Arrow* the inclined surface by which the surrounding pigment epithelium (*P*) delimit the lesion N nuclei Note that festoon like series of irregular nuclei or parts of lobed nuclei extend from the apical part of the pigment epithelial cell forming the border of the lesion into the retinal part of the lesion
× 1 00

Fig 22 Electron micrograph from the border of the 40 h old lesion in the pigment epithelium *P* pigment epithelial cell forming the border of the lesion *Solid arrows* the inclined lateral surface membrane delimiting the lesion *Open arrow* points to the plasma membrane of a cytoplasmic protrusion which containing a nucleus or part of a lobed nucleus (*N*) invade the retinal lesion from the apical part of the pigment epithelial cell
× 4200


N
N
P
9


N
P
20


21


N
P
22

extended as apical protrusions towards and into the lesions (Fig 29) Some of these apical cytoplasmic protrusions contained a nucleus or part of a lobed nucleus (Figs 18 22 30–31)

The nucleus containing apical cytoplasmic protrusions of the pigment epithelial cells around the lesions first appeared 32 h after irradiation Their number and volume increased during the second day after irradiation From the apical part of the pigment epithelial cells they extended towards the lesion where they continued apically to the disrupted pigment epithelium and ramified in the intercellular substance between the damaged outer segments of the photoreceptors (Fig 29) The nuclei of the protrusions were variously sized and shaped but otherwise appeared as pigment epithelium nuclei (Figs 18 22 30–31) The cytoplasm of the protrusions contained an elaborate system of agranular endoplasmic reticulum great amounts of polysomes many profiles of granular endoplasmic reticulum Golgi complexes mitochondria and small granular lamellar inclusions However the protrusions contained only a few melanin granules The amount of small granular lamellar inclusions decreased during the second day after irradiation The part of the protrusions situated outside the lesions appeared to push away the outer segments of the photoreceptors However the part of the protrusions situated within the lesions were moulded around or contained great amounts of structures which appeared as condensed and deformed pieces of the damaged outer segments of the photoreceptors

The retinal part of the lesions appeared to be invaded by a kind of cells which were classified as phagocytic This kind of cells first appeared singly 32 h after irradiation just apical to the pigment epithelium immediately surrounding the lesion (Fig 18) They were very similar to the nucleus containing apical cytoplasmic protrusions of the pigment epithelial cells and could be distinguished from them only by outlining the plasma membranes of the cells in serial sections

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Figs 19 20 & 21 Serial 1 μm sections from the border of the 40 h old lesion in the pigment epithelium *Arrow* the inclined surface by which the surrounding pigment epithelium (*P*) delimit the lesion N nuclei Note that festoon like series of irregular nuclei or parts of lobed nuclei extend from the apical part of the pigment epithalial cell forming the border of the lesion into the retinal part of the lesion
× 1[illegible]00

Fig 22 Electron micrograph from the border of the 40 h old lesion in the pigment epithelium *P* pigment epithelial cell forming the border of the lesion *Solid arrows* the inclined lateral surface membrane delimiting the lesion *Open arrow* points to the plasma membrane of a cytoplasmic protrusion which containing a nucleus or part of a lobed nucleus (*N*) invade the retinal lesion from the apical part of the pigment epithelial cell
× 4200



24

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In the 40 h old lesion the number of phagocytic cells was increased They were found singly or in small groups at the level of the outer segments of the photoreceptors near to the borders of the lesion in the pigment epithelium (Fig 23) In the 48 h old lesion the cells appeared in groups forming a nearly continuous layer across the lesion at the level of the outer segments of the photoreceptors (Fig 28) They were also found singly or in small groups at the level of the inner segments of the photoreceptors

The phagocytic cells contained a nucleus similar to those of the apical protrusions of the pigment epithelial cells around the lesions (Fig 24) At places their cytoplasm formed only a thin rim around the nucleus and thin irregular ramifications extended into the intercellular substance At other places their cytoplasm was more abundant and appeared very similar to that of the apical protrusions of the pigment epithelial cells The cytoplasm contained an elaborate system of agranular endoplasmic reticulum great amounts of polysomes and many profiles of granular endoplasmic reticulum Mitochondria and Golgi complexes were often found accumulated close to the nucleus (Figs 24–25) Microtubuli were often seen in the ramifications of the cells (Fig 27) When situated in groups the cells were closely related to each other but specialized junctional complexes between the cells were not found The plasma membrane of the cells was at places moulded around the remnants of the damaged tissue in the lesions (Figs 24–27) The cells also appeared to contain the remnants of the damaged tissue in cavities which were bounded by a membrane closely related to the endoplasmic reticulum and the Golgi complexes In other cavities of this type the contents appeared to be more or less disintegrated so that their origin was difficult or impossible to recognize However the melanin granules found in the cells or in their cavities appeared unchanged (Fig 26) Small granular lamellar inclusions or structures appearing as primary lysosomes were not found in the cells Occasionally the endoplasmic reticulum appeared to contain crystalline structures and a fibrillar material was seen in the intercellular substance close to the plasma membrane of the cells (Fig 27) Those cells situated farthest away from the borders of the lesion in the pigment epithelium commonly showed more abundant cytoplasm and contained greater amounts of the remnants of the damaged tissue than those cells situated nearest to the borders of the lesion in the pigment epithelium

The damaged tissue in the retinal part of the lesions appeared to be phagocytosed and progressively disintegrated by the apical cytoplasmic protrusions of the pigment epithelial cells around the lesions and by the invading phagocytic cells described above The part of the damaged tissue situated outside these cells appeared unchanged The disintegration involved predominantly the outer segments of the photoreceptors which were barely visible by light microscopy in the 48 h old lesion (Fig 28) Retinal oedema was not found in lesions more than 24 h old



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G

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Pl

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Fig 23 The border of the 40 h old lesion in ʰ pigment epithelium *Solid arrow* the inclined surface by which *the surrounding* pigment epithelium (*Ps*) delimit the lesion *Pl* disrupted pigment epithelium in the lesion N nuclei *Open arrows* point to the surface of the phagocytic cells
x 1 00

Fig 24 The phagocytic cells in the retinal part of the 40 h old lesion N nuclei M mitochondria *Solid arrows* structures which appear as more or less disintegrated rem nan s *of the damaged* tissue. *Open arrows* point to the plasma membrane of the cells O outer segments of the photoreceptors *Pl* disrupted pigment epithelium
x 1\$ 00

Fig 25 Another section of the phagocytic cells shown in Fig 24 *G Golgi com* plexes *Large arrow* points to a cavity containing structures which appear as more or less disintegrated remnants of the damaged tissue. Note that *the cells are closely* related to each other (*mall arrows*) but show no specialized junctional complexes
x 4600

Fig 6 From the phagocytic cells shown in Figs 24 25 The plasma membrane of the cell (*open arrow*) is moulded around the melanin granules (*curved arrow*) of the disrupted pigment epithelium (*Pl*) *Solid straight arrows* point to membrane bounded cavities containing structures which appear as more or less disintegrated remnants of the damaged tissue
0000

Fig Part of a ramification of the phagocytic cells shown in Figs 24-26 *I* inter cellular substance *mt* m rotubuli *Arrow* points to cavity containing structures which appear as more or less disintegrated remnants of the damaged tissue
x 4600

Insert top left fibrillar material in the intercellular substance close to the plasma membrane of the cell
x 5 000

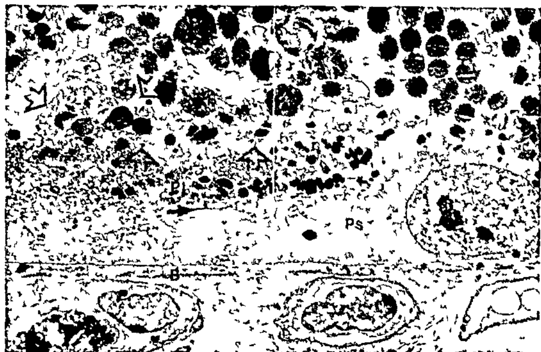
Insert bottom right crystalline structure in the endoplasmic reticulum of the cell
x 5 000

Fi 8 Part of the 48 h old lesion is shown n the right side of the figure *Solid rrow* the inclined surface by wh ch the surrounding pigment epithelium (*Ps*) del mit the lesion N nucleus situated in the apical part of the pigment epithelial cell forming the border of the lesion. *Open arrow* points to the surface of the phagocyt c cells
x 600

Fig 29 The border of the 48 h old les on in the pigment epithelium *Open arrows* point to the plasma membrane of a cytoplasmic protrusion which invade the les on from the ap cal part of the pigment epithelial cell (*Ps*) *S lid arrow* the inclined lateral surface membrane by wh ch the surrounding pigment epithelium (*Ps*) delimit the les o *Pl* disrupted pigment ep thelium in the lesion *B* Bruch s membrane
00

Fig 30 F om the p gment epithelium immediately outside the borders of the 48 h old lesion The pigment epithel al cell contains two nucle or a lobed nucleus (N) One of the nuclei or part of a lobed nucleus is situated in an apical cytoplasmic pro trusion apically to the lateral junctional complex (*J*) *B* Bruch s membrane
x 5500

Fig 31 Another sect on of the cell shown in F g 30 N nuclei *J* lateral junctional complex
5500







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Fig 3 The border of the 40 h old lesion in the pigment epithelium *Solid arrow* the incl ned surface by which the surrounding pigment epithelium (*Ps*) *delimit the lesion* *Pl* d srupted pigment epithelium in the lesion V nuclei *Open arrows* point to the surface of the phagocytic cells
1 00

Fig 24 The phagocytic cells in the retinal part of the 40 h old lesion N nuclei *M* mitochondria *Solid arrows* structures which appear as more or less disintegrated remnants of the damaged tissue *Open arrows* point to the plasma membrane of the cells O outer segments of the photoreceptors *Pl* disrupted pigment epithelium
× 13 00

Fig 25 Another section of the phagocytic cells shown in Fig 24 C Golgi complexes *Large arrow* points to a cavity containing structures which appear as more or less disintegrated remnants of the damaged tissue *Note that the cells are closely related to each other (small arrows)* but show no specialized junctional complexes
× 24600

Fig 6 From the phagocytic cells *shown in F gs 24–25* The plasma membrane of the cell *(open arrow) is moulded around the melanin* granules *(curved arrow)* of the d srupted pigment epithelium (*Pl*) *Solid straight arrows* point to membrane bounded cavities conta ning structures which appear as more or less di integrated remnants of the damaged tissue
0000

Fig 2 Part of a ramification of the phagocytic cells hown in Figs 24–26 *I* intercellular substance *mt* microtubuli *Arrow* points to cavity containing structures which appear as more or less disintegrated remnants of the damaged tissue
× 4600
Insert top left fibrillar material in the intercellular substance close to the plasma membrane *of the cell*
× 5 000
Insert bottom right crystalline structure in the endoplasmic reticulum of the cell
× 5 000

F 8 Part of the 48 h old lesion is shown in the right side of the figure *Solid arrow the incl ned surface* by which the surrounding pigment epithel um (*Ps*) delimit *the lesion* N nucleus situated in the apical part of the pigment epithelial cell forming the border of the lesion *Open arrow* points to the surface of the phagocytic cells
× 600

Fig 9 The border *of the 48* h old lesion in the pigment epithelium *Open arrows* point to the *plasma* membrane of a cytoplasmic protrusion which invade the lesion f om the *ap cal* part of the pigment epithelial cell (*Ps*) *Solid arrow* the *inclined* lateral surface membrane by which the surrounding p gment *epithel um (Ps) delimit the les on Pl* disrupted pigment epithelium in the lesion *B Bruch s* membrane
× 00

Fig 30 From the p gment epithel um immediately outside the borders of the 48 h old *les on* The pigment epithel al cell contains two nuclei or a lobed *nucleus* (*N*) *One of the nuclei* or part of a lobed nucleus is situated in an *apical cytoplasmic protrusion* apically to th lateral junctional complex (*J*) *B Bruch s* membrane
5500

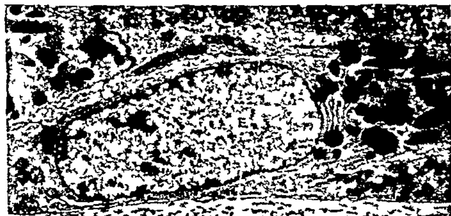
Fig 31 Another sect on *of the cell* shown in Fig 30 N nuclei *J* lateral *junctional* c mplex
5500

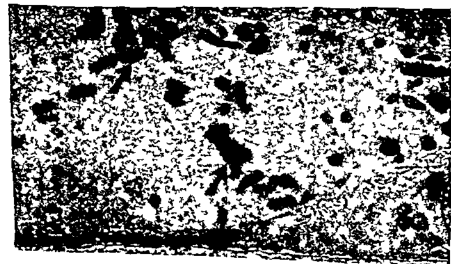
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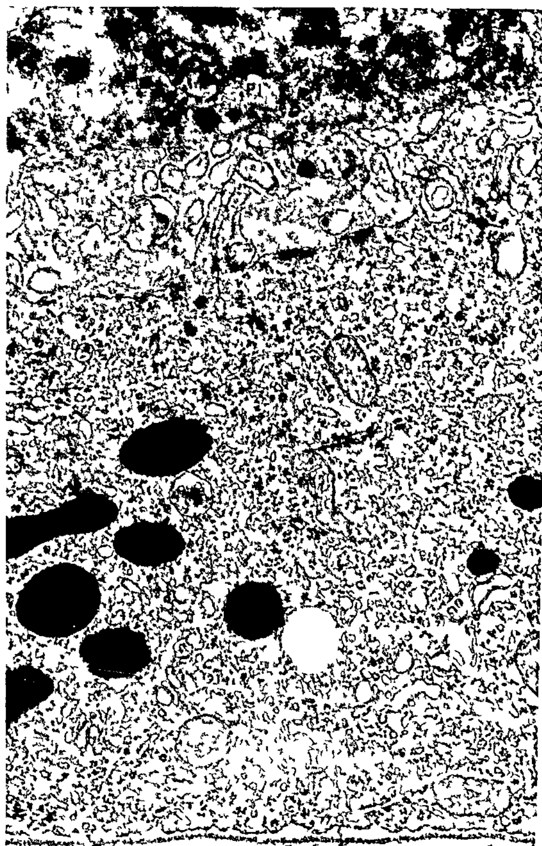
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P1
37
B



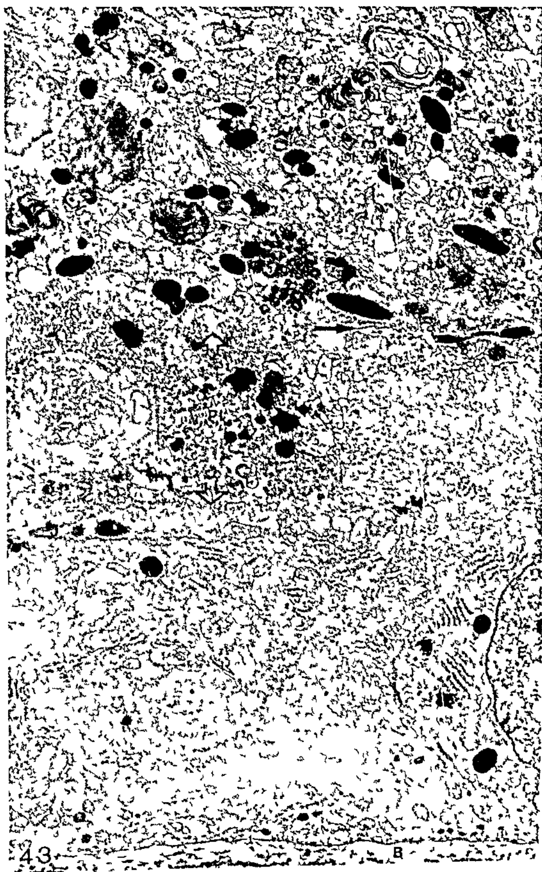
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Fig 32 The border of the 64 h old lesion in the pigment epithelium *Long arrow* Bruch s membrane *Short arrow* the inclined surface by which the surrounding pigment epithelium (to the right) delimit the lesion (to the left) *A* nucleus situated in an apical cytoplasmic protrusion of the pigment epithelium surrounding the lesion *D* nucleus of a phagocytic cell in the lesion *L* nucleus in the regenerated pigment epithelium in the lesion *C* cone nucleus
× 1500

Fig 33 The central part of the 64 h old lesion in the pigment epithelium *Long arrow* Bruch s membrane *D* nuclei of the phagocytic cells *E* nuclei in the regenerated pigment epithelium *Open arrows* point to the sufaces of the two kinds of cells *PI* disrupted pigment epithelium Note that the regenerated pigment epithelium is lower in the more central part of the lesion (the left side of the figure) than in the more peripheral part (the right side of the figure)
× 1500

Fig 34 The border of the 64 h old lesion in the pigment epithelium *B* Bruch s membrane *Solid arrows* the inclined lateral surface membrane by which the surrounding pigment epithelium (*Ps*) delimit the lesion *Open arrow* points to the plasma membrane of the regenerated pigment epithelium which is joined to the surrounding pigment epithelium (*Ps*) by the lateral junctional complex (*J*) *PI* disrupted pigment epithelium The continuation into the lesion from the left margin of the figure is shown in Fig 35 (superimpose *x*)
× 6300

Fig 35 The continuation into the lesion from the left margin of Fig 34 (superimpose x) *E* nucleus in the regenerated pigment epithelium *J* junctional complexes *Arrow* the inclined lateral surface membrane by which the surrounding pigment epithelium (to the right) delimit the lesion Note the shape of the cells The continuation into the lesion from the left margin of the figure is shown in Fig 36 (superimpose y)
× 6300

Fig 36 The continuation into the lesion from the left margin af Fig 35 (superimpose y) The cell of which the nucleus is seen in Fig 35 is continued as a thin cytoplasmic extension between Bruch s membrane and the next cell in the layer of regenerated pigment epithelium This next cell shows a mitotic figure (*arrows*)
× 6300

Fig 37 From the regenerated pigment epithelium in the central part of the 64 h old lesion The plasma membrane of the cell show small infoldings in the basal part facing Bruch s membrane (*B*) and small slender protrusions in the apical part facing the disrupted pigment epithelium (*PI*) Note that the cytoplasm of this kind of cells contains no structures which appear as the remnants of the damaged tissue
× 24600

Figs 38 & 39 Melanosomes in different stages of melanization *found in the basal* part of the regenerated pigment epithelium in the 64 h old lesion *B* Bruch s membrane
× 57000

Fig 40 From the phagocytic cells in the central part of the 64 h old lesion *D* nucleus *G* Golgi complexes *Solid arrows* point to cavities containing structures which appear as more or less disintegrated remnants of the damaged tissue *Open arrows* point to the plasma membrane *PI* disrupted pigment epithelium
x 6 00

Fig 41 Part of the 72 h old lesion *Large solid arrow* points to the inclined surface by which the surrounding pigment epithelium (to the right) delimit the lesion (to the left) *A* nucleus situated in an apical cytoplasmic protrusion of the surrounding pigment epithelium *Small solid arrow* points to a mitotic figure just inside the border of the lesion *D* nuclei of the phagocytic cells *E* nuclei in the regenerated pigment epithelium *C* cone nuclei *R* rod nuclei *Open arrow* retinal capillary *Ch* choriocapillaris
600

Fig 42 From the central part of the 72 h old lesion *Long arrow* Bruch s membrane *D* nuclei of the phagocytic cells *E* nuclei in the regenerated pigment epithelium *Open arrows* point to the surfaces of the two kinds of cells Between the open arrows is the remnants of the disrupted pigment epithelium
x 1500

Fig 43 From the central part of the 72 h old lesion *B* Bruch s membrane *E* nucleus in the regenerated pigment epithelium Note that this kind of cells are joined to each other by lateral junctional complexes (*J*) Note also that the regenerated pigment epithelium contain no structures which appear as the remnants of the damaged tissue whereas the cytoplasm of the phagocytic cells seen in the upper part of the figure (above the solid arrow) is loaded with such structures *Open arrows* point to the plasma membranes of the two kinds of cells In the left part of the figure the disrupted pigment epithelium (*PI*) is seen between the two kinds of cells In the right part of the figure the two kinds of cells are closely related to each other (*solid arrow*) but there are no specialized junctional complexes between the two kinds of cells
6300

Fig 44 The phagocytic cells in the 72 h old lesion from the same section as Fig 43 *D* nuclei *Open arrow* points to the plasma membrane The cytoplasm of the phagocytic cells contain varying amounts of structures which appear as more or less disintegrated remnants of the damaged tissue The cells are seen to extend in between two undamaged cone inner segments (*I*) Note that the phagocytic cells are closely related to each other but show no specialized junctional complexes
6300

Fig 45 From the phagocytic cells in the 72 h old lesion *G* Golgi complexes *Arrows* small granular lamellar inclusions
5 000

Fig 32 The border of the 64 h old lesion in the pigment epithelium *Long arrow* Bruch s membrane *Short arrow* the inclined surface by which the surrounding pig ment epithelium (to the right) delimit the lesion (to the left) *A* nucleus situated in an apical cytoplasmic protrusion of the pigment epithelium surrounding the lesion *D* nucleus of a phagocytic cell in the lesion *E* nucleus in the regenerated pigment epithelium in the lesion *C* cone nucleus
x 1500

Fig 33 The central part of the 64 h old lesion in the pigment epithelium *Long arro* Bruch s membrane *D* nuclei of the phagocytic cells *E* nuclei in the regenerated pig ment epithelium *Open arrows* point to the sufaces of the two kinds of cells *PI* dis rupted pigment epithelium Note that the regenerated pigment epithelium is lower in the more central part of the lesion (the left side of the figure) than in the more peripheral part (the right side of the figure)
x 1500

Fig 34 The border of the 64 h old lesion in the pigment epithelium *B* Bruch s mem brane *Solid arrows* the inclined lateral surface membrane by which the surrounding pigment epithelium (*Ps*) delimit the lesion *Open arrow* points to the plasma mem brane of the regenerated pigment epithelium which is joined to the surrounding pig ment epithelium (*Ps*) by the lateral junctional complex (*J*) *PI* disrupted pigment epithelium The continuation into the lesion from the left margin of the figure is shown in Fig 35 (superimpose x)
x 6300

Fig 35 The continuation into the lesion from the left margin of Fig 34 (superimpose x) *E* nucleus in the regenerated pigment epithelium *J* junctional complexes *Arrow* the inclined lateral surface membrane by which the surrounding pigment epithelium (to the right) delimit the lesion Note the shape of the cells The continuation into the lesion from the left margin of the figure is shown in Fig 36 (superimpose y)
x 6300

Fig 36 The continuation into the lesion from the left margin af Fig 35 (superimpose y) The cell of which the nucleus is seen in Fig 35 is continued as a thin cytoplasmic extension between Bruch s membrane and the next cell in the layer of regenerated pigment epithelium This next cell shows a mitotic figure (*arrows*)
x 6300

Fig 37 From the regenerated pigment epithelium in the central part of the 64 h old lesion The plasma membrane of the cell show small infoldings in the basal part facing Bruch s membrane (*B*) and small slender protrusions in the apical part facing the disrupted pigment epithelium (*PI*) Note that the cytoplasm of this kind of cells contains no structures which appear as the remnants of the damaged tissue
x 24600

Figs 38 & 39 Melanosome in different stages of melanization found in the basal part of the regenerated pigment epithelium in the 64 h old lesion *B* Bruch s mem brane
x 57000



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the disrupted pigment epithelium and most of the damaged outer and inner segments of the photoreceptors (Figs 41–42) The outer nuclear layer showed evidence of shrinkage but still contained a number of pyknotic nuclei In the sections perpendicular to the retinal plane the extent of the lesion in the outer nuclear layer was smaller than in the pigment epithelium and undamaged nuclei and inner segments of the surrounding photoreceptor cells were seen overlying the peripheral part of the lesion in the pigment epithelium

In the choroidal part of the lesions the inflammatory reaction and the occlusion of the choriocapillaris by inflammatory cells as seen the first two days after irradiation decreased during the third day The choriocapillaris was entirely open 72 h after irradiation (Figs 41–42)

5 *Changes from 3 days to 35 days after irradiation* (Comparison between the 3 day 4 day 6 day 9 day 13 day 18 day 25 day and 35 day old lesions)

The pigment epithelial cells in the zone about 75 μm wide around the lesions showed moderate changes from the third day after irradiation They often contained an irregular lobed nucleus situated in the basal part of the cell and additional nuclei situated in apical cytoplasmic protrusions which showed increasing volume and contained increasing amounts of melanin granules 3 to 9 days after irradiation (Figs 47 51–53) Mitotic figures were not seen From 9 to 35 days after irradiation no further changes were seen in the pigment epithelium around the lesions

The retinal part of the lesions was nearly filled by the two kinds of cells (a) phagocytic cells and (b) regenerated pigment epithelium which appeared to invade the lesions during the second and third days after irradiation In the 3 day old lesion these two kinds of cells were still more or less separated from each other by the remnants of the disrupted pigment epithelium (Figs 42–43) In the 4 to 35 day old lesions the phagocytic cells and the regenerated pigment epithelium were closely related to each other (Figs 46 53–55 57) Together they formed a cluster of cells which was closely related to the pigment epithelium around the lesions and extended from Bruch s membrane into the outer nuclear layer In this cluster of cells the regenerated pigment epithelium could be recognized as a basal layer of cells which were joined to each other and to the pigment epithelium around the lesions by lateral junctional complexes (Figs 53–55) The phagocytic cells showed no junctional complexes comparable to those of the pigment epithelium Between the regenerated pigment epithelium and the phagocytic cells no specialized junctional complexes were found

The phagocytic cells showed considerable changes from 3 to 9 days after irradiation During this period the phagocytic cells especially those situated at the level of the outer and inner segments of the photoreceptors contained decreasing amounts of the remnants of the damaged tissue (Fig 48) but in

Fig 46 Part of the 4 day old lesion is shown in the left side of the figure. *D* nuclei of the phagocytic cells *E* nuclei in the regenerated pigment epithelium *Open arrow* retinal capillary *S* synapses in the outer plexiform layer *Short arrow* outer limiting membrane *Long arrow* Bruch s membrane *V* vein in the choroid
× 3 5

Fig 47 From the border of the 9 day old les on in the pigment epithelium *Long arrow* Bruch s membrane *Short arrow* the inclined surface by which the surrounding p gment ep thelium (to the left) delimit the lesion (to the right) *A* nuclei situated in apical cytoplasm c protrusions of the surrounding pigment ep thelium *D* nucleus of a phagocytic cell *E* nucleus in the regenerated pigment epithelium
1 00

Fig 48 Fr m the phagocyt c cells in the central part of the 4 day old lesion *D* nucleus *G* Golgi complexes *M* mitochondria *Arrows* point to structures which appear as more or less d sintegrated melan n granules and other remnants of the damaged t ssue
× 24600

Fig 49 Small gran lar lamellar inclusions and melanosomes in different stages of melanizat on found in the phagocytic cells in the 4 day old les on *D* nucleus
24600

Fig 50 A labyr nth like system of interdigitating slender cytoplasmic protrusions (*a* u) by which two phagocytic cells are joined to each other From the 4 day old les on
4100

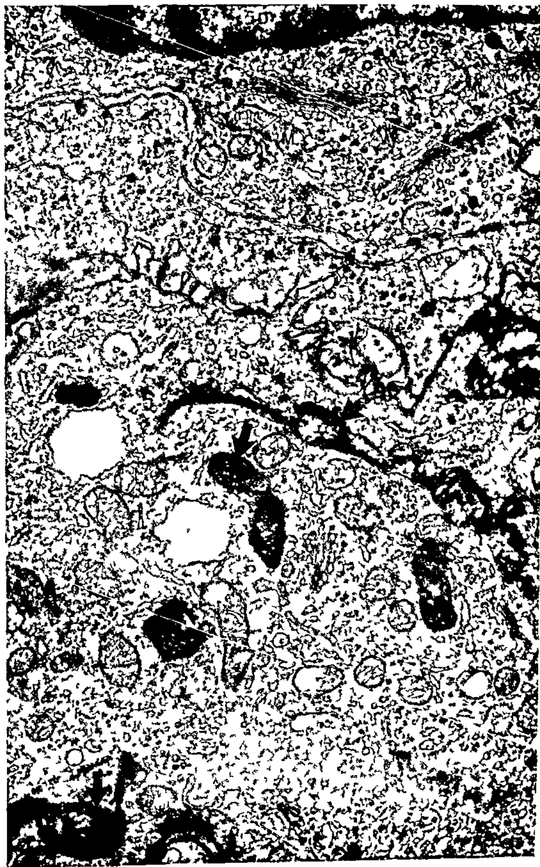
creasing amounts of small granular lamellar inclusions melanosomes in different stages of melanization melanin granules and compound inclusions (Figs 49 54–56) Lipofuscin like inclusions were rarely observed The accumulation of melanin granules appeared to be most pronounced in those cells facing the inner layers of the retina At this stage the phagocytic cells were often joined to each other by labyrinthe like systems of interdigitating slender protrusions (Figs 50 55) From 9 to 35 days after irradiation no further changes were seen in the phagocytic cells

The regenerated pigment epithelium showed moderate changes from 3 to 9 days after irradiation Often the cells were voluminous and contained great amounts of mitochondria (Figs 54–55) The amount of melanin granules in the cells was not increased in the older lesions melanin granules were found in lower amounts in the regenerated pigment epithelium than in the phagocytic cells From 9 to 35 days after irradiation the regenerated pigment epithelium appeared unchanged

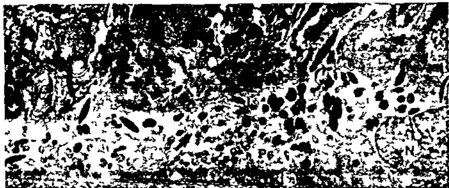
The disintegration of the damaged retinal tissue by the phagocytic cells as seen the second and third days after irradiation progressed The disintegration involved primarily the disrupted pigment epithelium and the outer and inner segments of the photoreceptors (Figs 46 57) the last remnants of these structures were seen by electron microscopy in or between the phagocytic cells 4 to 6 days after irradiation (Fig 48) In the outer nuclear layer the disintegration and shrinkage continued 25 days after irradiation the outer nuclear layer still contained a few pyknotic nuclei the undamaged nuclei of the surrounding photoreceptor cells were seen overlying the periphery of the lesion in the pigment epithelium

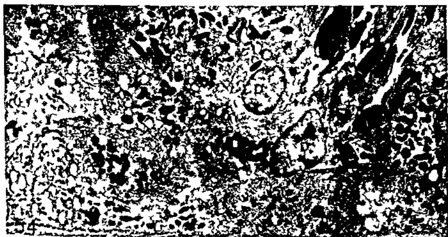
The choroidal part of the lesions showed some evidence of shrinkage from 3 to 35 days after irradiation but the choriocapillaris remained open (Figs 46 57)

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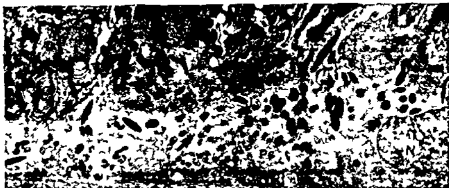
See text on page 45

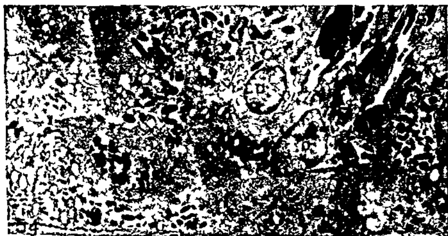




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Fig 51 The pigment epithelium about 50 μm outside the borders of the 9 day old lesion *N* lobed nucleus situated in the basal part of the pigment epithelial cell *A* nucleus situated in an apical cytoplasmic protrusion of the cell *Open arrows* point to the plasma membrane O outer segments of the photoreceptors
6300

Fig Another section of the pigment epithelial cell shown in Fig 51 Note the continuity of the cytoplasm between the nucleus situated in the basal part of the cell (*N*) and the nucleus situated in the apical protrusion (*A*)
x 24600

Fig 53 The border of the 9 day old lesion in the pigment epithelium *Arrow* the inclined lateral surface membrane by which the surrounding pigment epithelium (*Ps*) delimit the lesion *J* lateral junctional complex by which the surrounding pigment epithelium (*Ps*) is joined to the regenerated pigment epithelium in the lesion (to the left) *N* nucleus situated in the basal part of the pigment epithelial cell *A* nucleus situated in an apical cytoplasmic protrusion of the pigment epithelial cell *D* nucleus *of a phagocytic cell The continuation into the lesion from the left margin of the* figure is shown in Fig 54 (superimpose x)
x 6300 photographically reduced to x 3150

Fig 54 The continuation into the lesion from the left margin of Fig 53 (superimpose x) *D* nuclei of the phagocytic cells The continuation into the lesion from the left margin of the figure is shown in Fig 55 (superimpose y)
13 00 photographically reduced to x 3300

Fig 55 The continuation into the lesion from the left margin of Fig 54 (superimpose y) *B* Bruch s membrane *D* nuclei of the phagocytic cells *E* nucleus in the regenerated pigment epithelium The two kinds of cells are closely related to each other (*large arrow*) but there are no specialized junctional complexes between the two kinds of cells *Small arrows* point to the labyrinthe like systems of interdigitating protrusions by which the phagocytic cells are joined to each other *J* lateral junctional complexes of the regenerated pigment epithelium
x 13 00 photographically reduced to x 4100

Fig 56 Small granular lamellar inclusions melanin granules and compound inclusions found in the phagocytic cells in the 9 day old lesion *D* nucleus
x 4000

Fig The retina with the 9 day old lesion *Long arrow* Bruch s membrane *Short arrow* outer limiting membrane *S* synapses in the outer plexiform layer Note the shape and pigmentation of the scar tissue *and the shrinkage* in the outer nuclear layer
x 5

See text on page 51

Fig 1 The pigment epithelium about 50 μm outside the borders of the 9 day old lesion \ lobed nucleus situated in the basal part of the pigment epithelial cell A nucleus situated in an apical cytoplasmic protrusion of the cell Open arrows point to the plasma membrane O outer segments of the photoreceptors
x 6300

Fig Another section of the pigment epithelial cell shown in Fig 51 Note the continuity of the cytoplasm between the nucleus situated in the basal part of the cell (\) and the nucleus situated in the apical protrusion (\)
x 4600

Fig 3 The border of the 9 day old lesion in the pigment epithelium Arrow the inclined lateral surface membrane by which the surrounding pigment epithelium (Ps) delimit the lesion J lateral junctional complex by which the surrounding pigment epithelium (Ps) is joined to the regenerated pigment epithelium in the lesion (to the left) \ nucleus situated in the basal part of the pigment epithelial cell A nucleus situated in an apical cytoplasmic protrusion of the pigment epithelial cell D nucleus of a phagocytic cell The continuation into the lesion from the left margin of the figure is shown in Fig 54 (superimpose x)
x 6300 photographically reduced to x 31 0

Fig 4 The continuation into the lesion from the left margin of Fig 53 (superimpose I D nuclei of the phagocytic cells The continuation into the lesion from the left margin of the figure is shown in Fig 55 (superimpose))
x 15 00 photographically reduced to x 5300

Fig 5 The continuation into the lesion from the left margin of Fig 54 (superimpose I) B bruch s membrane D nuclei of the phagocytic cells E nucleus in the regenerated pigment epithelium The two kinds of cells are closely related to each other (large arrow) but there are no specialized junctional complexes between the two kinds of cells Small arrows point to the labyrinthe like systems of interdigitating protrusion by which the phagocytic cells are joined to each other J lateral junctional complexes of the regenerated pigment epithelium
x 15 00 photographically reduced to 4100

Fig 6 Small granular lamellar inclusions melanin granules and compound inclusions found in the phagocytic cells in the 9 day old lesion D nucleus
x 4000

Fig The retina with the day old lesion Long arrow Bruch s membrane Short arrow outer limiting membrane S synapses in the outer plexiform layer Note the shape and pigmentation of the scar tissue and the shrinkage in the outer nuclear layer
x 3

See text on page 1

the photoreceptor cells might as well be damaged by a primary effect of the Laser irradiation The damaging effect may thus be related to the normal response of the photoreceptor cells to light stimuli It may be suggested that the selective damage may be related to the sensitivity of the individual photoreceptor cells to the monochromatic light used in the Laser irradiation

It has been suggested that the cone cells may be more susceptible than the rod cells to Argon Laser irradiation (Tso et al 1973) and to moderate illumination from fluorescent lamps (Marshall et al 1972) but in the outer nuclear layer these studies showed no difference between rod and cone cells in acute lesions Similarly other studies on acute Laser lesions showed no evidence of differential damage of rod and cone cells (Marshall et al 1970) However in small 24 h old Helium Neon Laser lesions a relatively great number of pyknotic rod nuclei were found whereas the cone nuclei mostly were undamaged (Lappin & Coogan 1970) Recent studies also suggest that the cone cells may be more resistant than the rod cells to destruction by constant illumination from fluorescent lamps (La Vail 1976) The present observations on serial sections of acute lesions also suggest that most of the rod cells and a few of the cone cells were totally damaged by Ruby Laser irradiation The evaluation of these results must await further investigations on the above mentioned possible mechanisms of selective damage of the individual photoreceptor cells by light stimuli

The retinal oedema

Retinal oedema was previously found in 0 to 24 h old lesions which involved the pigment epithelium and photoreceptor cells (Lappin & Coogan 1970 Lerche 1973 Adams et al 1974) whereas there was no evidence of oedema in photoreceptor cell lesions with intact pigment epithelium (Kuwabara & Gorn 1968 Burger & Klintworth 1974) The retinal oedema found in the present study the first day after irradiation was limited to the damaged avascular layers of the retina The occurrence of the oedema may be related to the inflammatory reaction seen in the choroid However the junctional complexes between intact pigment epithelial cells may be regarded as a permeability barrier (Peyman & Bok 1972 Claude & Goodenough 1973 Hudspeth & Yee 1973 Feeney 1974 Peyman et al 1975 Smith & Rudt 1975 Leuenberger et al 19) and the pigment epithelium may be active in maintaining the normal homeostatic balance between the retina and the choroid Therefore it seems likely that the oedema found in the present study resulted from an impairment of the homeostatic balance between the retina and the choroid caused by the lesion in the pigment epithelium Similarly it is possible that the oedema disappeared in the older lesions because the homeostatic balance was reestablished by the pigment epithelium surrounding the lesion In this connexion the significance of the vacuoles seen in the endo

The damaging effect of Laser irradiation

The damage of the choroid and the outer layers of the retina caused by Laser irradiation is commonly ascribed to the absorption of radiant energy in the melanin granules resulting in heat production in the choroid and in the retinal pigment epithelium. The damage seen in the photoreceptor cell layers has been considered by a number of authors to be caused by this heating (Marshall 1970, Marshall & Mellerio 1970, Tso et al 1973, Goldman et al 1975, Marshall et al 1975). However a possible primary damage of the photoreceptor cells has been discussed in the case of Laser irradiation (Frisch et al 1971, Adams et al 1972, Gibbons & Allen 1977, Leuenberger et al 1977) as well as in the case of exposure to nearly monochromatic incoherent light (Sperling & Harwerth 1972).

In the present study the disruption of the choroidal melanocytes and the retinal pigment epithelial cells as well as the condensation of their cytoplasm and nuclear chromatin and the displacement of the cellular components are likely ascribed to the heating of the cells. In the peripheral part of the lesion in the pigment epithelium the distension of the endoplasmic reticulum without condensation of the cytoplasm may indicate that the cells were disrupted by heating of some other part of the individual cells or by heating of adjacent cells. In the pigment epithelium surrounding the lesions the inclination of the cells could be caused by the mechanical forces associated with the heating of the adjacent pigment epithelium. However the inclination of the cells might as well be caused by traction from the intact pigment epithelium surrounding the lesion.

In the outer nuclear layer some normal staining nuclei between the pyknotic nuclei were previously found in moderate and severe Laser lesions (Lappin & Coogan 1970, Marshall 1970, Goldman et al 1975, Marshall et al 1975). The limitation of moderate Laser lesions at the synaptic pedicles in the outer plexiform layer was also found previously (Ime & Geeraets 1965, Marshall 1970, Marshall & Mellerio 1970, Powell et al 1971, Wallow et al 1974, Marshall et al 1975). It was suggested by Marshall et al (1975) that the displacement of damaged cone fibers seen in the fibre layer of Henle may indicate a rapid intracellular degeneration of the individual cells.

In the present study a selective total damage of the individual photoreceptor cells was found whereas other photoreceptor cells within the irradiated area and the Muller fibres appeared undamaged. If it is assumed that the photoreceptor cells are damaged by the heating of the pigment epithelium this selective and total damage of some of the photoreceptor cells could be explained by the relations between the melanin granules and the individual photoreceptors (Tso et al 1973, Bulow 1975, Goldman et al 1975). However

poration of $[^{3}H]$thymidine but no mitotic figures However the possible process of amitotic proliferation was not followed

The possible origin of migrating phagocytic cells from the pigment epithelium is suggested by morphological similarity of the pigment epithelial cells and the phagocytic cells found in retinal lesions produced by Xenon arc photocoagulation of rabbit eyes (Gloor 1969) by cryotherapy of human eyes (Lerche 1972) and by retinal detachment in monkey eyes (Machemer & Laqua 1975) Based on the observations of pigment epithelial cells with apically placed nuclei and pigment epithelial cells with mitotic figures at the periphery of the lesions in rabbits treated with colchicin before fixation Gloor (1969) suggested two possibilities (1) that phagocytic cells may originate from the pigment epithelial cells with apically placed nuclei which were considered to detach from Bruch s membrane or (2) that phagocytic cells may originate from proliferating pigment epithelial cells These two possibilities could not be evaluated by Lerche (1972) as only 7 and 12 day old lesions were studied nor by Machemer & Laqua (1975) as many detached cells were found in the primary lesions Machemer & Laqua (1975) described phagocytic cells showing incorporation of $[^{3}H]$thymidine but no mitotic figures 3 days after retinal detachment and suggested that pigment epithelial cells may de differentiate into phagocytic cells However the process resulting in this de differentiation was not traced Furthermore the evaluation of the results was difficult as the lesions were invaded by inflammatory cells from the choroid or the retinal vessels (Gloor 1969 Machemer & Laqua 1975) and cells were found in Bruch s membrane (Lerche 1972)

The theory that pigment epithelial cells may de differentiate into phagocytic cells (Machemer & Laqua 1975) was to some extent supported as cell cultures derived from the pigment epithelium showed some evidence of cellular proliferation and phagocytic activity (Mandelcorn et al 1975 Mueller Jensen et al 1975) However it was difficult to exclude contamination by other type of cells during preparation Furthermore the two possibilities suggested by Gloor (1969) that phagocytic cells may originate either from detached or from proliferating pigment epithelial cells could not be evaluated as the cells were detached from Bruch s membrane during preparation Finally the process resulting in the de differentiation suggested by Machemer & Laqua (1975) of pigment epithelial cells into phagocytic cells was not traced in these studies either

The present observations on serial sections show that Bruch s membrane remained intact and that the retinal part of the lesions was not invaded by cells from the choroid nor from the retinal vessels The changes seen in the pigment epithelium around the lesions and in the retinal part of the lesions may be regarded as a sequence of events which has not been described previously representing stages of the process of wound healing of the avascular outer layers of the retina

plasmic reticulum of the pigment epithelium surrounding the oedematous lesions remains uncertain but similar vacuoles were described in frog skin epithelium in response to an impaired homeostatic balance (Voute et al 1975)

The distension and deformation of the outer segments of the photoreceptors seen in the oedematous lesions in the present study the first day after irradiation seem to correspond well to the changes described by other authors in response to osmotic stress (Cohen 1971 Heller et al 1971 Falk & Fatt 1973 Nir & Pease 1973)

These alterations of the outer segments of the photoreceptors may therefore indicate an impairment of the osmotic balance in the oedematous space of the retina

The process of wound healing of the retinal lesions

Tissue which morphologically appeared as proliferated pigment epithelium and phagocytic cells of uncertain origin has been described in a variety of pathological conditions and experimental retinal lesions of human as well as animal eyes It has been suggested that the pigment epithelial cells may proliferate and replace the damaged tissue (Lerche 1972 Tso 1973) and that migrating phagocytic cells may originate from the pigment epithelium (Cloor 1969 Lerche 1972 Machemer & Laqua 1975)

The consideration that pigment epithelial cells may proliferate in lesions of the outer layers of the retina was supported by the observation of mitotic figures at the periphery of 2–4 day old lesions produced by Xenon arc photocoagulation of the monkey retina (Ishikawa et al 1973 Wallow & Tso 1973 Ishikawa 1974) Furthermore in radioautographic studies the incorporation of [^{3}H]thymidine indicating DNA synthesis and cellular proliferation was found in the pigment epithelial cells showing mitotic figures in 7 day old lesions produced by Xenon arc photocoagulation of the rabbit retina (Inomata 1975) and by retinal detachment in monkey eyes (Machemer & Laqua 1975) However the mitotic figures and the incorporation of [^{3}H]thymidine was demonstrated only in the cells situated within the lesions Therefore these studies provide no informations about the process by which the cells possibly arose from the undamaged pigment epithelium

Other studies showed no evidence of rapid mitosis nor of incorporation of [^{3}H]thymidine during pigment epithelial regeneration after Laser and Xenon arc irradiation of the rabbit retina (Marshall & Mellerio 1970 Marshall et al 1971) As multinucleate lobed pigment epithelial cells with a nucleus in each lobe were occasionally found in these studies it was suggested that proliferation of pigment epithelial cells resulting in the regeneration of the pigment epithelium may occur by budding The possible amitotic proliferation of pigment epithelial cells was also discussed by other authors (Mueller Jensen et al 1975) as cell cultures derived from the pigment epithelium showed incor

cytic cells appeared to disintegrate the damaged tissue in membrane bounded intracellular cavities whereas the regenerated pigment epithelium showed no evidence of phagocytosis or intracellular disintegration of the damaged tissue The reasons why the two kinds of cells appeared so different even though both kinds appeared to arise from the pigment epithelium remain to be investigated Two major factors must be con d ~d (1) that both kinds of cells appeared to arise through a process of proliferation by budding and ( ) that the differentiation of the two kinds of cells may be influenced by their different location in the lesions In this context the possible role of the normalization of the choriocapillaris seen to occur simultaneously with the formation of the regenerated pigment epithelium must be taken into consideration

The phagocytic cells seen in the present study showed a number of changes which progressed with the age of the lesions It is interesting to note that small granular lamellar inclusions similar to primary lysosomes or micro peroxisomes (Leuenberger & Novikoff 1975 Robison & Kuwabara 1975) first appeared in the phagocytic cells as the process of intracellular disintegration of the damaged tissue appeared to be completed The evaluation of this observation must await further investigations on the function turnover and the possible storage of enzymes in lysosome like inclusions The hyperpigmentation seen in scars of the outer layers of the retina was by other authors not considered to be caused by melanogenesis even though incompletely melanized inclusions were found in the cells (Wallow & Tso 1973 Wallow et al 1973) However the present results indicate that as the disintegration of the damaged tissue was completed by the phagocytic cells they accumulated small granular lamellar inclusions melanosomes in different stages of melanization melanin granules and compound inclusions As the accumulation of these categories of inclusions may indicate melanogenesis in the adult (Bulow 1975) the present results suggest that melanogenesis was initiated in the phagocytic cells as the disintegration of the damaged tissue was completed The evidence of melanogenesis may be regarded as a further step in the differentiation of the phagocytic cells supporting the consideration that they originate from the pigment epithelium

In conclusion this study suggests that the process of wound healing of the avascular outer layers of the retina may occur without invasion of cells from the choroid nor from the retinal vessels It is suggested that the pigment epithelial cells around the lesion proliferate by the off budding of nucleus containing apical protrusions and that two kinds of cells arise through this proliferation (a) phagocytic cells which disintegrate the damaged tissue and as this process is completed show evidence of melanogenesis and (b) regenerated pigment epithelium which form a single cell layer along Bruch s membrane but show no evidence of phagocytosis or intracellular disintegra

The results indicate that during the first three days after irradiation the pigment epithelial cells around the lesions were changed into bi or multi nucleate cells with the additional nuclei situated in apical cytoplasmic pro trusions which extended towards and into the lesions There was no evidence neither of mitotic proliferation of the pigment epithelial cells nor of detach ment from Bruch s membrane of pigment epithelial cells with apically placed nuclei as suggested by Gloor (1969) On the other hand the cells found in the present study seem to correspond well to the multinucleate lobed pigment epithelial cells with a nucleus in each lobe which were occasionally found and suggested by Marshall et al (1971) to indicate that proliferation of pig ment epithelial cells occurs by budding

The phagocytic cells which in the present study appeared to invade the retinal lesions during the second and third days after irradiation were first seen just apical to the pigment epithelium around the lesion at the same site and at the same time as the first nucleus containing apical protrusions of the pigment epithelial cells The phagocytic cells and the nucleus containing apical protrusions of the pigment epithelial cells appeared very similar to each other and in many cases they could only be distinguished from each other by studying serial sections Thus the results of the present study seem to indicate that the phagocytic cells arose through the off budding of the nucleus containing apical protrusions of the pigment epithelial cells around the lesion

The regenerated pigment epithelium appeared in the present study to invade the retinal lesions as a single cell layer during the third day after irradiation The first cells seen in this layer were joined to the apical part of the sur rounding pigment epithelial cells and also appeared very similar to their nucleus containing apical protrusions Furthermore there was no evidence of lateral sliding of the pigment epithelium around the lesions Thus the results of the present study seem to indicate that also the regenerated pigment epi thelium arose through the off budding of the nucleus containing apical pro trusions of the pigment epithelial cells around the lesion

The observations by other authors of mitotic figures in the scar tissue (Ishi kawa et al 1973 Wallow & Tso 1973 Ishikawa 1974 Inomata 1975 Mi chemer & Laqua 1975) are also supported as both the phagocytic cells and the regenerated pigment epithelium found in the present study showed mitotic figures within the 64–72 h old lesions

The phagocytic cells and the regenerated pigment epithelium seen in the present study showed a number of characteristic differences The phagocytic cells were not joined to each other by junctional complexes comparable to those of the pigment epithelium whereas the regenerated pigment epithelium formed a single layer of cells which were joined to each other and to the surrounding pigment epithelium by lateral junctional complexes The phago

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tion of the damaged tissue Both the phagocytic cells and the regenerated pigment epithelium show evidence of further proliferation with mitotic figures

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tion of the damaged tissue Both the phagocytic cells and the regenerated pigment epithelium show evidence of further proliferation with mitotic figures

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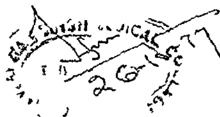
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UVEAL MELANOMA IN FINLAND

An epidemiological clinical histological and prognostic study

by

ILKKA RAIVIO



SCRIPTOR COPENHAGEN 1977

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I INTRODUCTION

Saving the sight as well as all functions of the eyes are indeed the main target of research and care for an ophthalmologist It is true that many general diseases often cause various kinds of ocular symptoms and eye examination is extremely important for differential diagnosis and control of some general diseases Yet it is only rarely that eye diseases cause any signs elsewhere in the body Malignant tumors in the eyes comprise a group of diseases where it is not only the sight of the eye but also the life of the patient at stake

Probably more than two thirds of intraocular malignant tumors are uveal melanomas It is a disease of primary importance for ophthalmologists

What is the nature of uveal melanoma? What has the patient to expect of the future?

The amount of pigment in skin hair and uvea defines certain racial qualities in man One of the strangest of these qualities is the possibility or tendency for malignant growth of the pigment cells It is a well known and as such surprising fact that members of the white race experience a greater risk than other races to develop a malignant pigmented tumor of the uvea a melanoma (Mann 1966) What are then the causes that lead to malignant changes in these cells if there is less pigment? The racial distribution is one of the peculiar qualities of this disease It is also a fact that there is evidently no final cure of this disease Metastases have been observed even as late as after a history of 36 years (Chisholm 1953 Newton 1965)

Uveal melanoma has been the subject of thorough and intense research for more than 100 years In most studies the main emphasis has been laid on the clinical and histopathological features of the disease as well as on the prognosis Epidemiological studies have been published from the Scandinavian countries (Ringertz et al 1960 Mork 1961 Jensen 1963)

The Finns are a marginal population Finland has a vast area low population density and national as well as areal isolation The Finns

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have their own gene inheritance that differs from other populations (Nevanlinna 1972, 1973)

What are then the distribution and nature of uveal melanoma in *Finland, in a country where the population according to Forsius et al* (1970) is one of the fairest in the world?

The purposes of this study are

1 To determine the incidence and the geographic distribution of the risk of uveal melanoma in Finland
2 To determine the clinical and histopathological picture as well as the prognosis of uveal melanoma in Finland
3 To study the differences in uveal melanoma between Finland and other countries

II REVIEW OF THE LITERATURE

1 EPIDEMIOLOGY

Cancer of the eye constitutes 0 15—0 8 % of all cancer in different countries (Doll et al 1970) In most statistics cancer of the eye is presented as one entity Thus it is difficult to determine the proportion of uveal melanomas compared to other eye tumors in a given country

Uveal melanoma is a disease of the white race (Mann 1966) It is a rarity in other races Paul et al. (1962) found that in a series of 2535 patients from all parts of USA only 11 were negroes It is 0 43 % of the material when blacks made about 10—11 % of the population in the United States On the basis of this the risk of uveal melanoma is 20 times higher in whites than in blacks in the United States The annual incidence rate was 0 49/100 000 for whites in Iowa in 1969—71 (Shammas & Watzke 1977) Uveal melanoma is rare in the yellow races as well No epidemiological studies on melanoma have been published from Japan but in all papers discussing sporadic cases or diagnostic methods it has been stated that the disease is there very rare (Fuchs 1962 Takajasu 1967 Takahashi et al 1969, Onuma & Tamura 1976) The same is true for china (Ling 1931 Cunningham 1952 Mann 1966) In an ophthalmic survey' from Polynesia there were no uveal melanomas but 70 conjunctival melanomas (Mann & Loschdorfer 1955) In India this disease seems to be extremely rare as well and report from India state that all cases have been Caucasians (Paul 1965 Das 1962) Although Paul s material of 104 melanomas originated from a hospital where the majority of the patients were Indians all melanoma cases were Caucasians

Melanoma is very rare also among African negroes Not a single uveal melanoma was found in a material of 312 eye tumors in Uganda (Templeton 1967) Quére et al (1964) studied 195 ocular tumors in Dakar and found 4 uveal melanomas Among the dark-skinned races in South America the disease is likewise very rare (de Buen 1973)

Numerous reports on uveal melanoma have been published from European countries as well as from the United States of America. Although only few detailed epidemiological studies are available it

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readily as the younger ones and thus their disease will not be diagnosed

From the point of view of an opthalmologist uveal melanoma is a very important disease In Europe and the United States 75—90 % of all ocular tumors (excluding tumors of the lids) are uveal melanomas In 10—20 % of all enucleations the underlying disease is melanoma (Dunphy et al 1958) According to Duke-Elder & Perkins (1966) 2—6 of every 10 000 ophthalmic patients have this disease

Jensen (1963) reviewed earlier studies on the frequency of uveal melanoma among ophthalmic patients and found that it varies from two to seven per 10 000 Already in 1928 Teraskeli reported this figure to be 5 per 10 000 in Finland

2 HISTOGENESIS

Many theories and discussions on the histogenesis of uveal melanoma have been published Jensen (1963) and Morgan (1973) have given a review to the earlier theories and research on histogenesis Masson (1926) showed that pigmented tumors of the skin were neither mesodermal nor epithelial in origin but neuroectodermal In 1937 Dvorak-Theobald came to the conclusion that all choroidal sarcomas originated from the Schwann cells and were of neuroectodermal origin Masson s hypothesis implied that pigment cells had an extrinsic origin and he suggested that they migrated from the central nervous system to the periphery as colorless cells which later on acquire pigment The migration from the neural crest has been demonstrated in animals (e g Brihaye-van Geertruyden 1963) Although this has not been directly demonstrated in man it can be regarded very probable (Greer 1967) Malignant melanoma originates from these melanocytes and is thus of neuroectodermal origin (Morgan 1973)

A much discussed question is whether uveal melanomas originate from pre-existing nevi or whether it is possible to have a melanoma de novo Most of the writers agree that a melanoma originates from a pre-existing nevus (Naumann et al 1966 Greer 1967 Yanoff & Zimmerman a b 1967 Albert et al 1974) Nevi of ohe choroid are very common Tamler & Maumenee (1959) and Jensen (1963) followed patients with choroidal nevi and did not find any noticeable growth in them The risk of a patient with a choroidal nevus to develop a melanoma in lifetime has been estimated to be approximately 1 % (Ganley & Comstock 1973) Although the eyes with melanoma have an excep-

seems that the risk of uveal melanoma does not largely differ among white populations (Benjamin et al 1948, Fuchs 1962, Paul et al 1962, Razumikhina 1962, Moron-Salas 1963, Frezotti & Guerra 1964, Gburkowa & Moskalowa 1966, Goder 1966, Holland 1967, Mondelski et al 1967, Donders 1973, Anton et al 1974, Barry 1973, Belan 1976 Shammas & Watzke 1977)

People in Northern Europe are very fair Thus the problems related to uveal melanoma in the Nordic countries are exceptionally interesting Jensen (1963) has published a review of the research on uveal melanoma in the Nordic countries In 1943—1952 an average of 28 melanomas were diagnosed annually in Denmark (Jensen 1963) In Norway the mean annual number of new cases of uveal melanoma in 1953—1960 was 21 According to Arnesen & Nornes (1975) the figure had increased to 28 new cases in 1960—1969 Ringertz et al (1960) reported that the number of new cases of eye melanoma in Sweden is 66 per year

Several reports have been published on sporadic familial aggregation of uveal melanoma (Davenport 1927, Bowen et al 1964, Lynch et al 1968, Tasman 1970) This is in accordance with the findings on cutaneous melanoma (Anderson et al 1967)

Jensen (1963) did not find any correlation between the color of iris and risk of contracting uveal melanoma On the other hand, Paul (1965) concluded that heavily pigmented eyes did not have as high incidence of melanoma as did the moderately pigmented eyes

Jensen (1963) found that most of the published materials showed a preponderance of females In the series from Finland presented by S Vannas (1969) 55 % of the patients were females Since very few materials have been presented with age-specific incidence rates of uveal melanoma the usefulness of the available data for international comparisons of the occurrence of uveal melanoma is rather limited

The risk increases and is highest in old ages However, melanomas have been reported also in children In the series of Paul et al (1962) four cases (0 1 %) were under the age of ten the youngest being five and Scheffer et al (1974) reported a malignant uveal melanoma in a two-year old infant In general less than 4 % of all cases are under the age of 30 and two thirds are above the age of 50 at the time of diagnosis A steep rise in the age-specific incidence rate has been observed from the age of 30 up to the age of 60—70 after which a decrease in the rate has been encountered (S Vannas 1959 Mork 1961 Jensen 1963 Shammas & Watzke 1977) Jensen has discussed this phenomenon and comes to the conclusion that the decline it not real it might depend on the fact that older people do not seek care so

classification (Lommatsch & Dietrich 1976 McLean et al 1977)

The main criticism against Callender s classification concerns the difference between spindle A and spindle B types It has been suggested that these types should be combined along with the group fascicular which is comprised of spindle cells On the other hand the group necrotic represents no morphological typing but only indicates that the tumor has been destroyed by necrosis (Jensen 1963)

The difference between various types when studied with light microscope is not reproducible in electron microscopy (François et al 1966 Iwamoto et al 1972) A conclusion has been drawn that different cell types in uveal melanoma actually do not represent different cells but different kinds of growth of the same cell in varying conditions This opinion is supported by results in tissue culture (Lund 1964 Irvine et al 1975) where the cells transformed from spindle cells to epithelioid type cells and vice versa depending on the quality of the growth conditions

Callender & Wilder (1935) and Callender et al (1942) found that reticulin content is a prognostically significant factor the prognosis is worse if there is less reticulin (less argyrophil fibres) in the tumor They also found that in the spindle cell tumors there is more reticulin than in melanomas composed of epithelioid-type cells The prognostic significance of reticulin content in uveal melanoma has subsequently either been confirmed (Paul et al 1962) or rejected (Jensen 1963 McLean et al 1977) Shammas & Blodi (1977) did not even include reticulin content in their multivariant analysis study

Pigment content of the tumor has for a long time been regarded a prognostic factor the darker the tumor the worse the prognosis (Wilder & Paul 1951 Jensen 1970 McLean et al 1977) The criteria of the pigment content vary in various papers McLean et al (1977) used only two groups light — heavy Shammas & Blodi (1977) had four different groups whereas Jensen (1963) divided his material into five categories It is thus very difficult to compare the relationship between the amount of pigment and prognosis in various researches However all researchists come to the conclusion that with an increasing amount of pigment the prognosis gets worse

Other prognostic factors are the size of the tumor and invasion of the tumor in the eye as well as the location of the tumor

Flocks et al (1955) reported a negative correlation between the volume of the tumor and the prognosis This finding has been confirmed in several studies the prognosis gets worse with increasing size of the tumor (Jensen 1963 Kramer & Lapiana 1976 McLean et al 1977 Shammas & Blodi 1977) McLean et al (1977) came to he

tionally high frequency of nevi, it is possible that these eyes develop melanoma because they have more melanocytes (Ganley & Comstock 1973)

3 HISTOLOGY AND OTHER PROGNOSTIC FACTORS

Several factors possess prognostic significance Von Hippel (1930—1933) found a significant correlation between the various stages of uveal melanoma (evaluated from histological specimens) and prognosis He divided the tumors into four stages on the basis of the growth of the tumor in the eye or extrabulbarly Teraskeli (1928) studied the prognosis of melanoma patients of the Helsinki University Eye Hospital The tumors were divided into four stages I no irritation, II glaucomatous stage, III extrabulbar growth and IV metastases The prognosis got worse in the order of the stages from I to IV S Vannas (1959) studied the prognosis of uveal melanoma in a series of 147 cases from the years 1925 to 1955, and found that the prognosis is correlated to the various stages described by von Hippel She recommended early enucleation, but also warned from unnecessary operations Patients who received postoperative X-ray treatment into the orbit experienced a better 5-year survival than the patients without radiotherapy

The spindle and round cell types were already known in the 19th century In 1931 Callender presented his classification of melanomas by cell type The six categories were as follows spindle A spindle B, fascicular, mixed, epithelioid, and necrotic He found that the prognosis was best in the spindle A group and became worse in the order stated above, being worst in the group necrotic

The principle of the Callender classification is generally accepted although many modifications of it exist It has been criticized for having too many types Differentiating between these is sometimes problematic in particular for unexperienced pathologist In 1958 Ashton suggested a classification on the basis of three main cell types spindle mixed and epithelioid Jensen (1970) suggested a limitation of cell types for practical reasons to differentiated group, anaplastic group and group between Morgan (1973) introduced the following classification predominantly spindle mixed and predominantly epithelioid type Simplified classifications have been adopted by many investigators (Jensen 1970 Arnesen & Nornes 1975 Shammas & Blodi 1977) but others continuously use the original Callender

classification (Lommatsch & Dietrich 1976, McLean et al 1977)

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The difference between various types when studied with light *microscope is not reproducible* in electron microscopy (François et al 1966 Iwamoto et al 1972) A conclusion has been drawn *that different cell types in* uveal melanoma actually do not represent different cells but different kinds of growth of the same cell in varying conditions *This opinion is supported* by results in tissue culture (Lund 1964 Irvine et al 1975) where the cells transformed from spindle cells to epithelioid type cells and vice versa depending on the quality of the growth conditions

Callender & Wilder (1935) and Callender et al (1942) found that reticulin content is a prognostically significant factor the prognosis is worse if there is less reticulin (less argyrophil fibres) in the tumor They also *found that in the spindle cell tumors there is more reticulin* than in melanomas composed of epithelioid-type cells The prognostic significance of reticulin content in uveal melanoma has subsequently either been confirmed (Paul et al 1962) or rejected (Jensen 1963 McLean et al 1977) Shammas & Blodi (1977) did not even include reticulin content in their multivariant analysis study

Pigment content of the tumor has for a long time been regarded a prognostic *factor* the darker the tumor the worse the prognosis (Wilder & Paul 1951 Jensen 1970 McLean et al 1977) The criteria of the pigment content vary in various papers McLean et al (1977) used only two groups light — heavy Shammas & Blodi (1977) had four different groups whereas Jensen (1963) divided his material into five categories It is thus very difficult *to compare the relationship* between the amount of pigment and prognosis in various researches However all researchists come to the conclusion that with an increasing amount of pigment the prognosis gets worse

Other prognostic factors are the size of the tumor and invasion of the tumor in the eye as well as the location of the tumor

Flocks et al (1955) reported a negative correlation between the volume of the tumor and the prognosis This *finding has been* confirmed in several studies the prognosis gets worse with increasing size of the tumor (Jensen 1963 Kramer & Lapiana 1976 *McLean et al* 1977 Shammas & Blodi 1977) McLean et al (1977) *came to* he

conclusion that not the volume but the area in the interior of the bulbus, measured with two largest diameters, is prognostically most significant According to Shammas & Blodi (1977) prognostically most important is the largest diameter that is in contact with the sclera McLean et al (1977) found that the size of the tumor is not prognostically as important a factor as e g the cell type The above mentioned papers also report that tumors in which the anterior border is located very anteriorly as well as high tumors have less favorable prognosis Small melanomas of the posterior choroid have better prognosis (Zimmerman 1973, Zimmerman & McLean 1975, Davidorf & Lang 1975)

Another prognostically significant factor is invasion of the tumor into the surrounding tissue Shammas & Blodi (1977) reported that rupture of the Bruch's membrane is an unfavourable prognostic sign All studies since von Hippel have agreed that prognosis is worse if extrabulbar growth can be demonstrated Donders (1973) has carefully studied and discussed the importance of intrascleral invasion According to him it is possible to find intrascleral invasion in all uveal melanomas provided a thorough enough examination is made On the basis of Donder's report one can conclude that the correlation between intrascleral invasion and prognosis entirely depends on the criteria of invasion Shammas & Blodi (1977) and McLean et al (1977) both found that intrascleral infiltration is a prognostically unfavourable sign The less differentiated tumors with rapid growth and invasive character are bound to have the worst prognosis (McLean et al 1977) Also have younger patients a better prognosis than the old ones (Paul et al 1962, Jensen 1963 Jensen 1970, Warren 1974 and Shammas & Blodi 1977)

4 DIAGNOSTIC METHODS AND TREATMENT

Ophthalmoscopy is the most important method in the diagnosis of uveal melanoma It has been improved by the use of both direct and indirect ophthalmoscopy as well as 3-mirror contactlens examination of the fundus Probably the most important among other diagnostic methods is diascleral illumination (M Vannas 1948) The difference between a total scotoma produced by a melanoma and a relative scotoma in case of a nevus is important in the differential diagnostics (Naumann et al 1966, Shields et al 1974 Oosterhuis et al 1976)

The role of fluorescein angiography in the diagnostics of uveal melanoma has also been discussed (Shields & McDonald 1974, Hayreh 1974 Laey 1976) Of particular interest are the methods which can be used even if the media are opaque One of these is the use of radioactive phosphorus (Jarret et al 1976) The intake of radio active phosphorus was greater in tumors which in histopathological examination showed more malignant features (Char et al 1976) Echography can be used irrespective of the visibility of the fundus (Oksala 1974 Hodes & Choromokos 1977) Computer tomography of the eye has been suggested for the diagnosis of intraocular tumors as well (Wollensack et al 1976)

Enucleation has been and still is the method of choice in the treatment of uveal melanoma, but in certain cases in particular in older patients enucleation is not the best method (Westerveld-Brandon & Zeeman 1957) Anderson & O Neil (1957) followed patients who had refused enucleation They found that the growth potential of the tumor may sometimes be very low However the natural history of uveal melanomas has not been fully clarified McLean et al (1977) suggested that in the cases of small posterior melanomas other methods of treatment should be considered Zimmerman & McLean (1975) did not recommend excision of the tumor because the tumor cells readily get into the blood stream. Photocoagulation and laser coagulation (Lund 1966 François 1974 Zimmerman & McLean 1975) or radiotherapy (Davidorf 1976 MacFaul & Morgan 1977) have also been suggested However a very careful selection of patients is required before decision is made in favor of nonoperative treatment Immunotherapy for uveal melanoma has lately been discussed by Leopold (1976) and clinical trials are in progress (Gorodilowa & Hollinshead 1975)

III PATIENTS AND METHODS

1 CANCER REGISTRY MATERIAL

The occurrence of uveal melanoma in Finland was analyzed by making use of the files of the Finnish Cancer Registry The Finnish Cancer Registry was established in 1952 and started collecting material in 1953 (Teppo et al 1975) *It is population-based and covers the* entire country The Registry receives reports on cancer cases from hospitals pathological laboratories and practitioners In addition, all death certificates issued in the country are annually checked against the files of the Registry

First, the annual numbers of new cases of histologically verified eye melanomas from the years 1953—1973 were drawn from the files of the Registry A total of 548 cases were found The material from 1972—1973 was examined more thoroughly to elucidate the distribution of the cases into melanomas of the uvea and conjunctiva Further analyses were performed on the assumption that the proportion of uveal melanomas from all melanomas of the eye remained constant through 1953—1973

2 CLINICAL MATERIAL

An attempt was made to compile a series of uveal melanoma from Finland which would represent the cases diagnosed in 1923—1966 as completely as possible The patient registers of all eye hospitals and departments of ophthalmology in the country were scrutinised This concerned the following hospitals

- *University Eye Hospital* Helsinki
- University Eye Hospital, Turku
- Eye *Department* Ceneral Hospital of Carelia Joensuu
- Eye Department Central Hospital of Kuopio
- Eye Department, Central Hospital of Central Finland Jyvaskyla
- Eye Department of the Deaconess Institution Lahti

— Eye Department Municipal Hospital Kivela Helsinki

In addition the melanoma cases of the following laboratories were collected

— Departments of Pathology University of Helsinki

— Department of Pathological Anatomy University of Turku

— Department of Forensic Medicine University of Helsinki

A total of 378 uveal melanoma cases were found, 359 were melanomas of the choroid or the ciliary body and 19 were melanomas of the iris In 370 cases the diagnosis had been verified histologically Five choroidal tumors and three tumors of the iris were included in the series on the basis of a very probable diagnosis the patients had refused the operation

The hospital records out patient charts and other documents concerning the patients were collected It was possible to gather a certain amount of information on all but one of the patients Also since the patients were from a long period of time and from many hospitals it was not possible to get all essential information on all of the patients

In order to find out the frequency of uveal melanoma among ophthalmic patients the files of the Helsinki University Eye Hospital in 1956—1965 as well as of one private ophthalmologist in Helsinki were checked

3 FOLLOW UP OF THE PATIENTS

The fate of the patients was studied by sending a personal letter to each of them If the patient was unable to answer the relatives were requested to answer the letter and inform whether the patient was alive or what was the time and cause of death If the letters were not answered the information concerning the address of the patient or possible time and cause of death was received from the local population registers A new letter was sent to the new address and the same information requested If the fate of the patient was not even then learned the time and the cause of death were cleared on the basis of information from census registers and the Finnish Cancer Registry

Finally the 10 year follow up of only 5 cases of choroidal or ciliary body melanomas was not cleared Three of them had emigrated and in two cases the identification of the patient was false or incomplete so that it was not possible to find them in any registers

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After exclusion of these 5 patients a total of 354 patients were left for survival analysis Two hundred and fourteen cases (60 %) were followed-up for at least 20 years, and 314 cases (89 %) for at least 15 years All of the 19 iris melanomas were followed

Information on the cause of death was established from three sources from the relatives, from various registers, and from death certificates In general, the information used was received from the relatives or various registers not from the certificates The cause of death had been listed principally in two ways death from metastases of the uveal melanoma or death from a cause other than melanoma Other cancers were here included in other causes" of death As deaths from metastases were accepted cases where the death certificate reported the primary cause of death to be melanoma of the eye As deaths from metastases were also accepted cases in which the relatives reported the patient s cause of death to be cancer in the liver, cancer in the abdomen or cancer all through the body The follow-up of the patients was calculated from the enucleation or if the patients refused operation, from the assessment of the clinical diagnosis

4 HISTOLOGICAL STUDY

The tissue specimens of 248 choroidal or ciliary body melanomas and those of 10 iris melanomas were obtained for histological re-examination In most instances the eye had been embedded in celloidin In a part of the more recent cases the eye had been embedded in paraffin Fifteen of the blocks of the choroidal and ciliary body melanomas were so hard that it was impossible to prepare them for a new histological examination Thus, 233 choroidal or ciliary body melanomas (65 % of the total) and 10 iris melanomas (53 %) were re-examined histologically

The histological specimens were melted and embedded in paraffin The blocks were resectioned and stained with hematoxylin and eosin as well as with Wilder silver stain (Callender & Wilder 1935) The silver staining was successful only in 188 cases (77 %) In those cases where the pigment content was so heavy that it was impossible to stuby the details of the tumor a bleaching was performed The cutting was done when possible in the center of the tumor The whole series was examined and all parameters recorded three times If the classification in these three examinations differed a renewed examination

Fig 1
Cell type predominantly spindle

Fig 2
Cell type mixed.

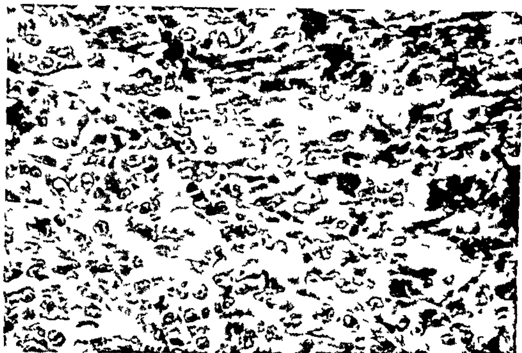


Fig 3
Cell type predominantly epithelioid

was performed In a few cases the classification was confirmed by other examinators

First, the size of the tumor was noted by measuring the two largest diameters by an accuracy of 1 mm In order to assess the extent of the tumor it was studied whether there was any infiltration in to the sclera or extrabulbar growth, or whether the Bruch s membrane was ruptured or intact

The following classification of the cell type of the tumor was applied

1) Predominantly spindle tumors consisting predominantly of spindle-shaped cells with a roundish nucleus (Fig 1)
2) Mixed tumors consisting of a combination of spindle-shaped and epithelioid-type cells (Fig 2) The amount of each type of cells in this category is nearly equal or varies from one part of the tumor to another so that it is not possible to classify the tumor into groups predominantly spindle or predominantly epithelioid
3) Predominantly epithelioid tumors consisting predominantly of large, roundish cells with marked cellular polymorphism (Fig 31) Mitotic figures occur in these cells much more frequently than in the spindle-shaped cells the nuclei are large hyperchromatic and have a conspicuous nucleolus

Both pigment and reticulin contents were estimated so that the scala from absence to heaviest pigment and reticulin content was roughly divided into three categories They were classified as low, medium and heavy (Fig 4)



Fig 4
Reticulin content medium to heavy

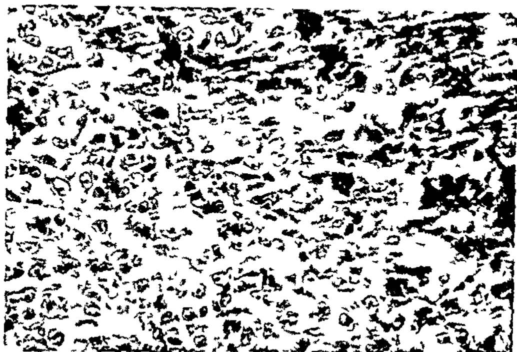


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Fig. 4
Reticulin content medium to heavy

IV RESULTS AND DISCUSSION

A Melanoma of the choroid and the ciliary body

1 EPIDEMIOLOGY

RESULTS

The mean annual number of histologically verified eye melanomas reported to the Finnish Cancer Registry in 1953—1973 was 26 (Table I) This means that the mean annual (crude) incidence of eye melanoma in Finland was 0 53/100,000 person-years The annual number of new cases showed a slight increase with time, most of this increase can be accounted for by the increase in the old age groups of the population Analysis of the Registry material from

Table I
Mean annual numbers of histologically verified eye melanomas reported to the Finnish Cancer Registry in 1953—1973

Year	No of melanomas
1953—1956	74
1957	13
1958	27
1959	35
1960	25
1961	27
1962	28
1963	25
1964	31
1965	24
1966	33
1967	28
1968	31
1969	38
1970	31
1971	23
1972	27
1973	28
Total	548

1972—1973 revealed that out of 55 eye melanomas 47 (85 %) were located in the uvea 1 (2 %) in the conjunctiva and in 7 (13 %) cases the location of the tumour in the eye was not defined Hence the annual incidence of uveal melanoma in Finland can be estimated to 0 5/100 000 person years

The distribution of the 359 melanomas of the choroid and ciliary body of the clinical material by the year of diagnosis is given in Table II A distinct increase in the annual number of cases with time is observable However comparison of the figures of Table II with the estimated annual numbers of new cases of uveal melanoma in the Cancer Registry material indicates that not all cases diagnosed in Finland had been entered in the clinical material of this survey

The age and sex distribution of the 359 melanomas of the choroid and ciliary body is presented in Table III There were 166 males (46 %) and 192 females (54 %) in the series The oldest patient wa

Table II

Distribution of the patients with choroidal and ciliary body melanomas, by the year of diagnosis and sex

Years	Males	Females	Total	Annual no of cases
1923—1936	13	11	24	1 7
1937—1946	25	27	52	5 2
1947—1956	60	72	133	13 3
1957—1966	68	82	150	15 0
Total	166	192	359	8 2

Table III

Distribution of the patients with choroidal and ciliary body melanomas, by age and sex

Age	Males	Females	Total
—29	6 (4 %)	9 (5 %)	15 (4 %)
30—39	21 (13 %)	17 (9 %)	38 (11 %)
40—49	27 (16 %)	30 (16 %)	58 (16 %)
50—59	49 (30 %)	49 (26 %)	98 (28 %)
60—69	38 (23 %)	54 (28 %)	92 (26 %)
70—	25 (15 %)	33 (17 %)	58 (16 %)
Total	166 (100 %)	192 (100 %)	359 (100 %)

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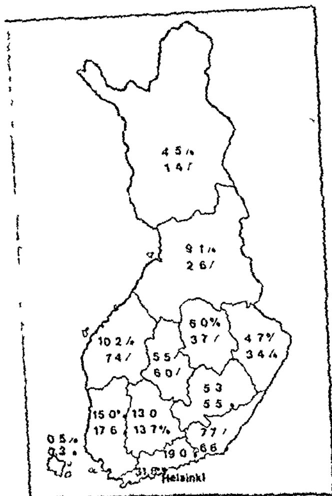


Fig 6
Distribution of the material into the various provinces of Finland. Upper figure distribution of the total population in 1960 *Lower figure distribution* of the material

northern Finland are included the material that have come to the south for treatment

In 1956—1965 about 30 000 patients were treated in the Helsinki University Eye Hospital 92 of these had uveal melanoma The proportion of melanoma patients was thus about 30/10 000 During the same period there were 300 000 out patient visits in the Eye Clinic Hence the frequency of melanoma among these patients was about 3 10 000

an 87-year-old man and the youngest a 19-year-old woman The median age was 55 years in males and 57 years in females The mean age for males was 54 6 years, that for females 55 7 years Only 4 % of the patients were under the age of 30, compared to 69 % in age groups over 50

The calculation of the age-specific incidence rates of melanomas of the choroid and ciliary body was based on the estimated total annual incidence of 0 5/100,000 person-years obtained from the figures of the Cancer Registry and on the age distribution of the present clinical material for 1947—1966 The population used in this calculation was the weighted mean population of Finland in 1947—1966 (Central Statistical Office 1948—1967) The risk of melanoma of the choroid and ciliary body was low in younger age groups and increased rapidly with age (Fig 5) In age group under 30 the incidence rate was 0 03 and in age group of 70 years and over 2 1/100,000 person years No difference in the risk was observable between the two sexes

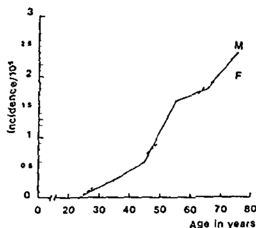


Fig 5
Mean annual age specific incidence rates (per 10^5) of choroidal and ciliary body melanomas in Finland in 1947—66 by sex

The percentage distribution of the material into various provinces in Finland by the domicile of the patients is presented in Fig 6 In southern Finland in the catchment area of the Helsinki University Central Hospital the proportion of melanoma cases is higher than the proportion of the population The opposite situation is observable in northern Finland It seems that most of the melanoma cases from southern Finland have been found whereas only those cases from

correlation with latitude This held true also after restricting the analysis to European countries only The results were similar when the information of the WHO computerized cancer data bank was used (Hakulinen et al 1977) mortality from eye cancer in adults exhibited a positive correlation with the distance from the equator

The high incidence and mortality rates of eye cancer in adults and consequently the rates of uveal melanoma as well in the Nordic countries can partly be accounted for the fact that reporting and registering of cancer cases is a well-established system in these countries and more complete reporting can be assumed to take place here as compared to most of the other countries in the world On the other hand racial differences and differences in the amount of melanin in the uvea may also be important. Nevanlinna (1972) has discussed the exceptional characteristics of the Finns as a population with the uniform and uncommon gene inheritance Another racial quality of the Finns is that they are one of the fairest people in the world (Forsius et al 1970) The risk of uveal melanoma shows a predilection of the white race (Mann 1966) and thus this disease is diagnosed very infrequently in the races with darker skin The details of the pathogenesis of melanoma and the role of melanin in it are unknown

The risk of uveal melanoma in Finland and in most other countries has remained rather stable during the last two decades An increasing trend in the rates of eye cancer in adults has been observed in Denmark beginnig in the 1950s and a decrease has taken place in Connecticut (Hakulinen et al 1977) Due to the diagnostic difficulties and gradual development of new medical facilities long term analyses of the trend in the risk of uveal melanoma are largely unreliable

No clues for the etiology of uveal melanoma could be discovered in this study The geographic differences in the risk which could reflect differences in etiological factors (sunlight, standard of living etc) were inconclusive since during the observation period the medical facilities and especially ophtmalmological services were unevenly distributed in the country and underdiagnostics certainly had existed in the northern parts of Finland On the other hand it is interesting that no changes with time in the risk could be established in Finland During the same time marked changes have taken place in the environment (urbanization) and customs This suggests that the risk factors of uveal melanoma probably are not determined by man This is in accordance with the observation that

Among the 8,000 patients recorded in the files of a practicing ophthalmologist in Helsinki there were four uveal melanomas (5/10,000)

The social classes applied in this survey were those defined by Nieminen (1958) 'upper class", i e persons in leading positions, "middle class" including farmers, and 'working class' The information given on the hospital records was used as such without further clarifications The distribution of the patients into these three classes is given in Table IV For reference, the distribution of the total Finnish population (Nieminen 1958) is also presented The distribution of the patients closely corresponded to that of the total population

Table IV
Distribution of the patients with choroidal and ciliary body melanomas and that of the total population into social classes

Social class [1]	Melanoma patients	Total population [1]
Upper class	3 %	3 %
Middle class	40 %	42 %
Working class	57 %	55 %
Total	100 %	100 %

[1] Nieminen 1958

DISCUSSION

Melanoma of the choroid and ciliary body is a rare disease In Finland, it constitutes only 0 2 % of all cancers The mean annual incidence in Finland (0 5/100,000 person-years) is approximately the same as has been reported from other Nordic countries (Ringertz et al 1960, Mork 1961, Jensen 1963) In the age groups over 15 the incidence and mortality of uveal melanoma can roughly be estimated on the basis of the figures for all cancers of the eye because melanoma of the uvea generally constitutes some 80—90 % of all malignant tumors of the eye in adults In international comparisons concerning the incidence (and mortality) of eye cancer in adults the Nordic countries stand very high in rank order (Doll et al 1970 Hakulinen et al 1977) Hakulinen et al (1977) were able to demonstrate that the incidence of eye cancer in adults shows a positive

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Table V
Presenting symptoms of the 359 patients with choroidal and ciliary body melanomas.

Sign	No of cases		%
Decreased visual acuity[1]	247		69
with pain		64	
with shadow		24	
with distortion of picture		23	
with inflammation		3	
with other symptoms		10	
Pain[1]	87		24
Distortion of picture[1]	46		13
with decreased visual acuity		23	
Shadow[1]	24		7
Accidental finding[1]	9		3
Inflammation[1]	4		1
Other symptoms	12		3
No information	15		5

[1] Alone or in combination with some of the other signs

decreased visual acuity one-half of these had a combination of two or more signs. Pain was next in order (24 %) followed by distortion of the picture (13 %) and a shadow (7 %)

The duration of the symptoms is presented in Table VI In one fifth of the cases the signs had been present for more than one year in 51 % of the cases the duration had been less than 4 months

The most important signs are given in Table VII Decreased visual acuity was the symptom for which 2/3 of the patients consulted doctor Visual acuity at the time of the initial examination is given in Table VIII Twenty-one per cent of the eyes were totally blind On the other hand 14 patients exhibited a normal visual acuity

Information on the visual field examination was available in 127 cases (Table VIII) A scotoma was found in 119 cases In 8 cases no visual field defect could be demonstrated It is possible that the less accurate Maggiore perimeter had been used in these cases On the other hand it is possible that due to the anatomical location of the tumor the scotoma could not be found with a perimeter

The hospital records contained information on the presence or absence of inflammatory signs (iridocyclitis) in 155 eyes Flare

the distribution into social classes of the present material closely corresponded to that of the general population

A female preponderance (54 %) was observed among the patients in the present series The same has been repeatedly observed previously (S Vannas 1959, Jensen 1963) However, if the age-adjusted rates are calculated, the reverse is true the age-adjusted incidence rate of eye cancer in males in age groups over 15 exceeds that of the rate in females in most countries The ratio of males to females of the rates in adults generally ranges from 1 0 to 1 5, in the 1950s and 1960s the ratio was 1 2 for Finland and Denmark 1 1 for Sweden and 1 3 for Norway (Hakulinen et al 1977)

Because only a few series of uveal melanoma have been published representing all cases within a given geographical area, the information on the age-specific incidence rates of uveal melanoma is scanty In all areas, the risk in children has been reported to be low (Paul et al 1962, Jensen 1963, Lommatsch & Dietrich 1976) The risk increases in middle-age and is highest in old age A certain leveling-off (as in females in this series) and even a decrease in the risk has been demonstrated in advanced age (S Vannas 1959, Jensen 1963, Shammas & Watzke 1977) However, due to difficulties in obtaining reliable figures in these age groups the decrease in the risk probably is an artifact

In Finland 2/3 of the patients were over 50 years of age The age distribution of the cases depends on the age structure of the general population, and calculations and comparisons of mean ages of patient series is perhaps not very fruitful From a practical point of view it is important to know that in young adulthood and early middle-age the chance of contracting a melanoma is low The risk of this disease increases among older patients In general the frequency of patients of uveal melanoma among all out-patients of an eye clinic or among patients consulting a practising ophthalmologist in Finland is expected to be not higher than 3—5/10 000 which corresponds to the figure reported from other countries (Jensen 1963 Duke-Elder & Perkins 1966)

2 CLINICAL PICTURE

RESULTS

The presenting symptom of the 359 patients in the clinical material are listed in Table V Two-thirds of the patients complained of

Table V
Presenting symptoms of the 359 patients with choroidal and ciliary body melanomas

Sign	No of cases		%
Decreased visual acuity [1]	247		69
with pain		64	
with shadow		24	
with distortion of picture		23	
with inflammation		3	
with other symptoms		10	
Pain [1]	87		24
Distortion of picture [1]	46		13
with decreased visual acuity		23	
Shadow [1]	24		7
Accidental finding [1]	9		3
Inflammation [1]	4		1
Other symptoms	12		3
No information	15		5

[1] Alone or in combination with some of the other signs

decreased visual acuity one-half of these had a combination of two or more signs. Pain was next in order (24 %) followed by distortion of the picture (13 %) and a shadow (7 %)

The duration of the symptoms is presented in Table VI In one-fifth of the cases the signs had been present for more than one year in 51 % of the cases the duration had been less than 4 months

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Information on the visual field examination was available in 127 cases (Table VII) A scotoma was found in 119 cases In 8 cases no visual field defect could be demonstrated It is possible that the less accurate Maggiore perimeter had been used in these cases On the other hand it is possible that due to the anatomical location of the tumor the scotoma could not be found with a perimeter

The hospital records contained information on the presence or absence of inflammatory signs (iridocyclitis) in 155 eyes Flare,

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2 CLINICAL PICTURE

RESULTS

The presenting symptom of the 359 patients in the clinical material are listed in Table V Two-thirds of the patients complained of

Table VIII
Visual acuity of 3.9 patients with choroidal and ciliary body melanomas.

Visual acuity	No of cases	%
≧1 0	14	4
0 9 —0 6	33	9
0 5 —0 1	91	25
0 05—1/~	124	35
0	77	21
No information	20	6
Total	359	100

precipitates and/or cells in the anterior chamber were regarded as signs of inflammation Inflammation was observed in 14 % of choroidal melanomas compared to 31 % in the melanomas of the ciliary body (Table VII)

The intraocular tension had been measured in 297 cases (Table VII) In 216 (73 %) cases it was normal (< 30 mmHg)

Diagnostic methods All patients in this material had been examined by direct ophthalmoscopy In the most recent cases as well as in the very early cases indirect ophthalmoscopy had been used lately with the binocular ophthalmoscope of Scheppens The Goldmann 3 mirror lens had also been used in later cases

Diascleral illumination was performed in 198 cases with 180 positive and 18 negative findings (Table IX) Table IX also lists the possible reasons for the negative results

Table IX
Findings of the diascleral illumination in patients with choroidal and ciliary body melanomas.

Result of diascleral illumination		No of cases
Positive		180
Negative		18
anterior location	7	
opaque media	3	
very small tumor	3	
posterior pole	2	
No information		161
Total		359

Table VI

Duration of symptoms of patients with choroidal and ciliary body melanomas

Duration of symptoms	No of cases	%
< 1 month	75	23
1— 3 months	68	21
4—12 months	122	37
> 1 year	66	20
No information	28	
Total	359	100

Table VII

Objective signs at the time of examination (other than visual acuity) in 359 patients with choroidal and ciliary body melanomas

Sign	Choroidal melanomas	Ciliary body melanomas	Total
Visual field			
Normal			8
Scotoma			119
Not stated			232
Inflammation			
Present	22 (14 %)	5 (31 %)	27
Not present	117 (86 %)	11 (69 %)	128
Not stated	182	22	204
Intraocular tension			
Normal			216
Elevated			81
Not stated			62
Finding in diascleral illumination			
Shadow			180
No shadow			18
Not stated			161
Finding in echography			
Positive			6
Negative			1
Not examined			352

Table VIII

Visual acuity of 359 patients with choroidal and ciliary body melanomas

Visual acuity	No of cases	%
≧1.0	14	4
0.9—0.6	33	9
0.5—0.1	91	25
0.05—1/∞	124	35
0	77	21
No information	20	6
Total	359	100

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No information		161
Total		359

Echography was performed in 7 cases, in 6 cases the diagnosis of tumor had been confirmed In the seventh case there was a small melanoma in the posterior pole of the bulbus, also diascleral illumination gave no shadow in this case Due to the retrospective nature of the material, no evaluation or comparison of the various diagnostic methods is possible

Blind eyes Ninety-one eyes were classified in the group of a "blind painful eye' Criteria for this category were visual acuity 0 or less than 0 05, elevated intraocular tension and opaque media In 70 cases pain had been recorded Fourty-six of the patients were males, 41 were females Two-thirds of the patients were over 60 and 1/4 over 70 years of age (Table X) The mean age of the patients in this group was 62 4 years as compared to 55 3 years in the total material

Table X
Distribution of the patients with blind painful eye by age

Age	No of cases	%
—29	1	1
30—39	3	2
40—49	12	13
50—59	15	16
60—69	31	34
70—	29	32
Total	91	100

DISCUSSION

Two-thirds of the patients with melanoma of the choroid and ciliary body complained of decreased visual acuity as their main symptom, and only 4 % of the patients had a normal visual acuity Pain was the symptom of one fifth of the patients The distribution of the symptoms in the present series closely corresponds to that reported from other countries (Jensen 1963 Warren 1974)

The duration of the symptoms was about the same as that observed by Jensen (1963) in Denmark However Jensen had 28 % of patients with past history longer than one year In this series there were 20 % of patients who had had the symptoms more than a year Possible and probable differences in the recording of the duration of symptoms must of course be borne in mind

Twenty-one per cent of the eyes with melanoma of the choroid and ciliary body were totally blind at the time of the initial examination This is in accordance with figures reported by Jensen (1963) and Zimmerman (1973) Patients with blind painful eyes were older than the rest of the material This suggests that older patients with melanoma of the eye are more ignorant of their symptoms On the other hand the delayed diagnosis may at least in some instances be attributable to diagnostic difficulties, since conventional methodology i e ophthalmoscopy and diascleral illumination cannot be applied if the media are opaque (Shields et al 1977) In these cases all possible diagnostic methods should be used echography (Oksala 1974 Hodes & Choromokos 1977) radiophosphorus examination (Char et al 1976) and computerized axial tomography (Wollensack et al 1976) Not infrequently a choroidal or ciliary body melanoma is found in an eye which has been enucleated due to blindness and pain even if no suspicion of a tumor existed The opposite is also true if the diagnosis had not been reached with certainty the number of unnecessary enucleations may increase (Vannas 1959 Jensen 1970) If the media are clear and the correct diagnosis is in doubt it is justified to follow the patient by making use of repeated photography and fluorescein angiography Since the collection of patients in this study terminated in 1966 the above mentioned new diagnostic methods had not been applied

According to Jensen (1963) the frequency of elevated intraocular tension among patients with melanoma of the choroid and ciliary body in earlier reports shows a wide variation ranging from 27—68 % In Jensen s (1963) own series the frequency was 36 % which is higher than the figure in this material (27 %) This does not necessarily depend on the criteria applied since in 68 ca es out of 81 the tension was 40 mmHg or over and only in 13 cases moderately elevated (30—39 mmHg)

The frequency of inflammatory disorders in the eye was 14 % in the present material and 15 % in the series of Jensen (1963) Inflammation was observable in 31 % of the eyes with melanoma in the ciliary body This difference is not readily explainable

3 HISTOLOGY

RESULTS

Location Histological examination of the 354 choroidal and ciliary body melanomas had shown that 38 (11 %) of the tumors were in the

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70—	29	32
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3 HISTOLOGY

RESULTS

Location Histological examination of the 354 choroidal and ciliary body melanomas had shown that 38 (11 %) of the tumors were in the

ciliary body and 316 in the choroid In five cases where enucleation was not done the tumor was clinically observed to be in the choroid

If the 19 iris melanomas are taken into account, the ciliary body melanomas constituted 10 % of all melanomas of the uvea

On the basis of the histological specimens it was possible to define the exact location of the tumor in 142 instances out of 233 107 tumors were located in the posterior part and 7 tumors in the anterior part of the bulbus while 28 melanomas (12 %) originated in the ciliary body

Cell type Distribution of the 233 histologically examined tumors by cell type is presented in Table XI Tumors composed predominantly of spindle-cells constituted 38 % of the series, 44 % were of mixed type and 19 % were composed predominantly of epithelioid-type

Table XI

Distribution of the choroidal and ciliary body melanomas by cell types of the tumor and sex

Cell type	Males	Females	Total
Predominantly spindle	38 (36 %)	48 (39 %)	86 (38 %)
Mixed	46 (44 %)	54 (44 %)	100 (44 %)
Predominantly epithelioid	21 (20 %)	22 (18 %)	43 (19 %)
Total	105 (100 %)	124 (100 %)	229 (100 %)
Not classifiable			4

Table XII

Distribution of the choroidal and ciliary body melanomas by age of the patient and cell type of the tumor

Age	Cell type			Total
	Predominantly spindle	Mixed	Predominantly epithelioid	
—29	1 (1 %)	3 (3 %)	—	4
30—39	8 (9 %)	12 (12 %)	3 (7 %)	23
40—49	12 (15 %)	18 (18 %)	7 (16 %)	37
50—59	31 (36 %)	25 (25 %)	10 (23 %)	66
60—69	22 (25 %)	26 (26 %)	12 (28 %)	60
70—	12 (14 %)	16 (16 %)	11 (26 %)	39
Total	86 (100 %)	100 (100 %)	43 (100 %)	229

cells Patients with epithelioid cell type tumors were older than those belonging to other groups (Table XII) The mean age of the patients in the three groups were as follows spindle-cell type 56 5 years mixed type 55 4 years and epithelioid cell type 59 6 years The distribution of the tumors by cell type was similar in both sexes (Table XI)

Pigment content The 233 tumors were classified into three groups according to the pigment content of the tumor cells as follows pigment content low in 98 cases (42 %) medium in 64 cases (28 %) and heavy in 69 cases (30 %), in two instances the classification proved unsuccessful

Table XIII
Distribution of the choroidal and ciliary body melanomas by cell type of the tumor and pigment content of the tumor cells

Cell type	Pigment content			Total
	Low	Medium	Heavy	
Predominantly spindle	44 (51%)	22 (22%)	21 (24%)	87 (100%)
Mixed	35 (36%)	31 (32%)	31 (32%)	97 (100%)
Predominantly epith	18 (42%)	9 (21%)	16 (37%)	43 (100%)
Total	97 (43%)	62 (27%)	68 (30%)	227 (100%)

Table XIV
Percentage distribution of the pigment content of tumor cells in both sexes and various age groups (227 choroidal and ciliary body melanomas)

Pigment content	Males	Females	Age						Total
			—29	30—39	40—49	50—59	60—69	70—	
Low	43	42	25	59	55	37	41	34	42
Medium	32	24	50	14	28	32	20	39	28
Heavy	25	34	25	27	18	32	39	27	30
Total	100	100	100	100	100	100	100	100	100

The distribution of the pigment content in the tumors of different cell types (Table XIII) showed that the highest percentage of low pigment content was found in spindle-cell type tumors whereas the highest proportion of heavy pigment content was observable among melanomas composed predominantly of epithelioid type cells No

consistent pattern emerged from the analysis of the correlation between the pigment content of the tumor cells and the sex or age of the patients (Table XIV) The mean ages of the patient in the low, medium and heavy pigment content groups were 55 0 years 57 8 years and 58 2 years, respectively

Table XV

Distribution of choroidal and ciliary body melanomas by cell type and reticulin content of the tumor

Cell type	Reticulin content			Total
	Low	Medium	Heavy	
Predominantly spindle	*18 (26%)*	*17 (25%)*	*33 (49%)*	*68 (100%)*
Mixed	23 (27%)	40 (48%)	21 (25%)	84 (100%)
Predominantly epith	11 (31%)	18 (50%)	7 (19%)	36 (100%)
Total	52 (28%)	75 (40%)	61 (32%)	188 (100%)

Table XVI

Percentage distribution of the reticulin content of tumor tissue in both sexes and various age groups *(188 choroidal and ciliary body melanomas)*

Reticulin *content*	*Males*	*Females*	Age						Total
Low	33	29	50	32	31	29	32	19	29
Medium	44	38	25	26	52	41	32	53	41
Heavy	24	33	25	42	17	30	36	28	31
Total	100	100	100	100	100	100	100	100	100

Table XVII

Percentage distribution of the size of the tumor in both sexes and various age groups (227 choroidal and ciliary body melanomas)

Tumor size	Males	Females	Age						Total
			-29	30-39	40-49	50-59	60-69	70-	
Small (< 38 mm)	34	34	—	35	51	36	28	27	34
Medium (38—74 mm)	29	29	40	48	24	36	31	22	29
Large (≧ 75 mm)	38	37	60	17	24	28	53	51	37
Total	100	100	100	100	100	100	100	100	100

The staining for *reticulin fibers* was performed in 188 cases The reticulin content of the tumor tissue was classified as low in 52 cases medium in 75 cases and heavy in 61 cases (Table XV) Tumors composed predominantly of epithelioid-type cells contained less reticulin fibers than did other types (Table XV) The distribution of the reticulin content exhibited no differences between the two sexes or between the various age groups (Table XVI) The mean ages of patient with tumors of low medium and heavy reticulin content were 54 9 years 57 6 years and 56 8 years respectively

The size of the tumor was calculated by measuring the two largest diameters in a section The tumors were divided into three categories < 38 mm 38—74 mm² and ≧ 75 mm² The distribution of the tumor size in various age groups (Table XVII) revealed that in the age groups over 60 there were more large tumors than in the younger age groups the distributions were similar in both sexes

Extent of the tumor Invasion of the tumor in the sclera and rupture of the Bruch s membrane by tumor tissue were examined in sections made from the center of the tumor Possible extrabulbar growth was also recorded In judging the invasion into the sclera only those findings were classified as invasion where the sclera was deeply infiltrated by melanoma cells but growth through the sclera was not encountered If only few cells were seen in the sclera the case was excluded from the group deep scleral invasion

No invasion was observed in 35 % of the tumors The Bruch s membrane was ruptured in 50 % of the eyes while deep scleral invasion and extrabulbar growth were encountered infrequently that is in 7 % and 8 % of the tumors respectively The extent of the tumor growth could not be assessed in 10 instances

DISCUSSION

The histological diagnosis of melanoma of the uvea is not difficult but the pathologist should attempt to evaluate all details which are relevant in terms of the outcome of the patient in question.

Various classifications of uveal melanoma by cell types have been introduced (Callender 1931 Ashton 1958 Jensen 1963 1970 Morgan 1973 Arnesen & Nornes 1975 and others) Most of them include among others spindle cell and epithelioid cell tumors although the detailed criteria of different categories often vary However these two types of melanoma cells are not probably basically different observations made in tissue culture and electron microscopy support

consistent pattern emerged from the analysis of the correlation between the pigment content of the tumor cells and the sex or age of the patients (Table XIV) The mean ages of the patient in the low, medium and heavy pigment content groups were 55 0 years, 57 8 years and 58 2 years, respectively

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Cell type	Reticulin content			Total
	Low	Medium	Heavy	
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Low	33	29	50	32	31	29	32	19	29
Medium	44	38	25	26	52	41	32	53	41
Heavy	24	33	25	42	17	30	36	28	31
Total	100	100	100	100	100	100	100	100	100

Table XVII
Percentage distribution of the size of the tumor in both sexes and various age groups (227 choroidal and ciliary body melanomas)

Tumor size	Males	Females	Age						Total
			-29	30-39	40-49	50-59	60-69	70-	
Small (< 38 mm²)	34	31	—	35	51	36	28	27	34
Medium (38—74 mm²)	29	29	40	48	24	36	31	22	29
Large (≧ 75 mm)	38	37	60	17	24	28	53	51	37
Total	100	100	100	100	100	100	100	100	100

studies comparisons of the distribution of the pigment content between the materials from various areas are not justified

The tumors with predominantly epithelioid cells contained less argyrophil fibres than spindle-cell tumors This agrees with the observations made e g by Callender & Wilder (1935) Due to difficulties in the definition and assessment of low medium and heavy reticulin content comparisons with other materials are not fruitful

In the present material ciliary body tumors constituted 10 % of all melanomas of the uvea According to the review of Jensen (1963) the average proportion of ciliary body melanomas in different studies was 8 % Jensen also reviewed earlier studies on the anatomic distribution of choroidal melanomas 63 % were located in the posterior part of the eye 23 % in the middle part and 17 % in the anterior part of the bulbus Six per cent of the choroidal melanomas of this material were found in the anterior part of the eye (assessed from the histological specimens) and up to 94 % were located posteriorly

The extent of the tumor inside the eye can be evaluated by two criteria is there invasion into the sclera and is the Bruch s membrane intact or ruptured? Most of the patients with uveal melanoma seek medical care so early that the extrabulbar growth is rarely seen The frequency of intrascleral invasion was 50 % in the series of Brihaye-van Geertruyden (1963) and 52 % in the material reported by Jensen (1963) Donders (1973) initially found intrascleral invasion in 30 % of his cases but after making use of serial sections the figure increased to 80 % In the present study deep scleral infiltration was observed only in 7 % of the eyes The differences presented above can largely be accounted for by the differences in the criteria applied in the assessment of the invasion of melanoma cells into the sclera

The Bruch s membrane was ruptured in 50 % of the cases in the present material Jensen (1963) reported a frequency of 42 % and Flocks et al (1955) 66 % Flocks et al (1955) suggested that the Bruch s membrane ruptures more readily in old individuals due to the fragility of the membrane in advanced age

4 PROGNOSIS

RESULTS

Prognosis of the patients was evaluated in three ways 1) Crude survival rates were calculated as percentages of the patients alive of the total number of patients followed up 2) Percentages of deaths

this opinion It seems that the cell types present in a given melanoma are determined by the growth characteristics of the tumor In slowly-growing neoplasms the cells are tightly packed and spindle-shaped If the tumor starts to grow more rapidly, the cells take a roundish, epithelioid-type shape The spindle cells have been interpreted to be well differentiated whereas the epithelioid-type cells would represent a less differentiated type (Jensen 1963) It is easy to understand why tumors of purely spindle-cell or epithelioid-cell type are rare

For practical purposes, introduction of a more flexible classification with groups such as predominantly spindle-cell , ' predominantly epithelioid-cell ' and "mixed-cell ' type seems to be well justified It was also followed in this study The reproducibility of this classification can be satisfactory in the hands of one examiner — as was the case in this study However, due to the difficulty to exactly define the term "predominantly , the observer variation must be great Comparisons between various studies are thus difficult and in many instances impossible For example, the proportion of epithelioid-cell type tumors was 3 % in the series of Paul et al (1962) and 9 % in the material presented by Warren (1974) In both these studies the epithelioid-cell type was defined as being composed entirely of epithelioid-type cells If the group has been defined as predominantly epithelioid , the frequency has varied between 12 % (Jensen 1963) and 37 % (Goder 1966) In the present material the figure was 19 % Similar differences can be shown in the frequencies of spindle-cell and mixed types It appears that the possible real differences in the distribution of the different types of uveal melanoma between countries and especially between areas with high and low incidence cannot be assessed properly unless one and the same examiner reclassifies the histological specimens of all materials to be compared

Occurrence of melanin is a very characteristic feature of melanoma cells, although totally amelanotic tumors can be found also in the uvea While no differences existed in the pigment content between both sexes or between various age groups, the frequency of heavy pigment content was highest among epithelioid-cell type tumors and that of low pigment content among spindle-cell type tumors This is a very interesting finding since it means that the melanin content of the cells increases with the process of dedifferentiation A conclusion may be drawn that the concepts well differentiated and less differentiated in connection with spindle-cell and epithelioid cell type melanomas are perhaps incorrect Since the criteria of the various groups of melanin content varies in the different

studies comparisons of the distribution of the pigment content between the materials from various areas are not justified

The tumors with predominantly epithelioid cells contained less argyrophil fibres than spindle-cell tumors This agrees with the observations made e g by Callender & Wilder (1935) Due to difficulties in the definition and assessment of low medium and heavy reticulin content comparisons with other materials are not fruitful

In the present material ciliary body tumors constituted 10 % of all melanomas of the uvea According to the review of Jensen (1963) the average proportion of ciliary body melanomas in different studies was 8 % Jensen also reviewed earlier studies on the anatomic distribution of choroidal melanomas 63 % were located in the posterior part of the eye 23 % in the middle part and 17 % in the anterior part of the bulbus Six per cent of the choroidal melanomas of this material were found in the anterior part of the eye (assessed from the histological specimens) and up to 94 % were located posteriorly

The extent of the tumor inside the eye can be evaluated by two criteria is there invasion into the sclera and is the Bruch s membrane intact or ruptured? Most of the patients with uveal melanoma seek medical care so early that the extrabulbar growth is rarely seen The frequency of intrascleral invasion was 50 % in the series of Brihaye-van Geertruyden (1963) and 52 % in the material reported by Jensen (1963) Donders (1973) initially found intrascleral invasion in 30 % of his cases but after making use of serial sections the figure increased to 80 % In the present study deep scleral infiltration was observed only in 7 % of the eyes The differences presented above can largely be accounted for by the differences in the criteria applied in the assessment of the invasion of melanoma cells into the sclera

The Bruch s membrane was ruptured in 50 % of the cases in the present material Jensen (1963) reported a frequency of 42 % and Flocks et al (1955) 66 % Flocks et al (1955) suggested that the Bruch s membrane ruptures more readily in old individuals due to the fragility of the membrane in advanced age

4 PROGNOSIS

RESULTS

Prognosis of the patients was evaluated in three ways 1) Crude survival rates were calculated as percentages of the patients alive of the total number of patients followed up 2) Percentages of deaths

Table XVIII

Results of 3 5 10 15 and 20 year follow-up of patients with choroidal and ciliary body melanomas by age and sex

	Males	Females	Age —29	30-39	40-49	50-59	60-69	70-	Total
3 yr follow up									
Alive	122 (75%)	146 (76%)	14 (93%)	32 (94%)	46 (81%)	76 (78%)	69 (75%)	31 (53%)	268 (76%)
Dead (other cause)	6 (4%)	10 (5%)	—			1 (1%)	3 (3%)	12 (21%)	16 (5%)
Dead (metastases)	35 (21%)	35 (18%)	1 (7%)	2 (6%)	11 (19%)	21 (21%)	20 (22%)	15 (26%)	70 (20%)
Total	163	191	15	34	57	98	92	58	354
5 yr follow up									
Alive	93 (57%)	107 (56%)	10 (67%)	24 (71%)	41 (72%)	59 (60%)	49 (53%)	17 (29%)	200 (57%)
Dead (other cause)	15 (9%)	14 (7%)	—	—	—	2 (2%)	10 (11%)	17 (29%)	29 (8%)
Dead (metastases)	55 (34%)	70 (36%)	5 (33%)	10 (29%)	16 (28%)	37 (38%)	33 (35%)	24 (41%)	125 (35%)
Total	163	191	15	34	57	98	92	58	354
10 yr follow up									
Alive	67 (41%)	73 (38%)	10 (67%)	19 (56%)	33 (58%)	40 (41%)	28 (30%)	10 (17%)	140 (40%)
Dead (other cause)	21 (13%)	23 (12%)	—	1 (3%)	—	5 (5%)	17 (18%)	21 (36%)	44 (12%)
Dead (metastases)	75 (46%)	95 (50%)	5 (33%)	14 (41%)	24 (42%)	53 (54%)	47 (51%)	27 (47%)	170 (48%)
	163	191	15	34	57	98	92	58	354
15 yr follow up									
Alive	39 (28%)	43 (25%)	9 (60%)	17 (52%)	19 (40%)	21 (24%)	14 (17%)	2 (4%)	82 (26%)
Dead (other cause)	26 (18%)	37 (21%)	1 (7%)	1 (3%)	1 (2%)	10 (12%)	25 (31%)	25 (50%)	63 (20%)
Dead (metastases)	76 (54%)	93 (54%)	5 (33%)	15 (45%)	28 (58%)	55 (65%)	43 (53%)	23 (46%)	169 (54%)
Total	141	173	15	33	48	86	81	50	315
20 yr follow up									
Alive	20 (21%)	22 (19%)	7 (64%)	7 (32%)	12 (35%)	8 (14%)	7 (13%)	1 (3%)	42 (20%)
Dead (other cause)	21 (22%)	29 (25%)	1 (9%)	1 (5%)	1 (3%)	10 (18%)	19 (34%)	18 (51%)	50 (23%)
Dead (metastases)	56 (58%)	66 (56%)	3 (27%)	14 (64%)	21 (62%)	38 (69%)	30 (54%)	16 (46%)	122 (57%)
Total	97	117	11	22	34	56	56	35	214

from metastases were calculated by the total number of patients followed-up 3) Corrected survival rates in which deaths from causes other than metastases of the melanoma were excluded were also calculated and used especially for comparisons between groups which differed in respect of age

Whole material sex age In the present material 354 patients were followed up for at least 10 years 314 patients for 15 years and 211 patients for 20 years. The three-year crude survival rate was 76% the 5-year rate was 56% and the 10 year rate 40% (Table XVIII Fig 7) No difference was observable in the survival rates between males and females (Table XIX) During the follow-up time of the 10 years 48% of the patients died from metastases of their melanoma the corrected 10 year survival rate thus being 52%

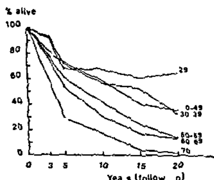


Fig 7
Crude survival rates of patients with choroidal and ciliary body melanomas in Finland in 1923—1966 by age

Table XIX
Crude and corrected survival rates (in per cent) of patients with choroidal and ciliary body melanomas, by sex

Follow up time	Males		Females		Total	
	Crude	Corrected	Crude	Corrected	Crude	Corrected
3 years	75	79	76	82	76	80
5 years	57	66	56	64	56	65
10 years	41	54	38	50	40	52
15 years	28	46	25	46	26	46
20 years	21	42	19	44	20	43

Table XVIII

Results of 3 5 10 15 and 20 *year follow*-up of patients with choroidal and ciliary body melanomas by age and sex

	Males	Females	Age						Total
			—29	30-39	40-49	50-59	60 69	70-	
3 yr follow up									
Alive	122 (75%)	146 (76%)	14 (93%)	32 (94%)	46 (81%)	76 (78%)	69 (75%)	31 (53%)	268 (76%)
Dead (other cause)	6 (4%)	10 (5%)	—			1 (1%)	3 (3%)	12 (21%)	16 (5%)
Dead (metastases)	35 (21%)	35 (18%)	1 (7%)	2 (6%)	11 (19%)	21 (21%)	20 (22%)	15 (26%)	70 (20%)
Total	163	191	15	34	57	98	92	58	354
5 yr follow up									
Alive	93 (57%)	107 (56%)	10 (67%)	24 (71%)	41 (72%)	59 (60%)	49 (53%)	17 (29%)	200 (57%)
Dead (other cause)	15 (9%)	14 (7%)	—	—	—	2 (2%)	10 (11%)	17 (29%)	29 8%)
Dead (metastases)	55 (34%)	70 (36%)	5 (33%)	10 (29%)	16 (28%)	37 (38%)	33 (35%)	24 (41%)	125 (35%)
Total	163	191	15	34	57	98	92	58	354
10 yr follow up									
Alive	67 (41%)	73 (38%)	10 (67%)	19 (56%)	33 (58%)	40 (41%)	28 (30%)	10 (17%)	140 (40%)
Dead (other cause)	21 (13%)	23 (12%)	—	1 (3%)	—	5 (5%)	17 (18%)	21 (36%)	44 (12%)
Dead (metastases)	75 (46%)	95 (50%)	5 (33%)	14 (41%)	24 (42%)	53 (54%)	47 (51%)	27 (47%)	170 48%)
	163	191	15	34	57	98	92	58	354
15 yr follow up									
Alive	39 (28%)	43 (25%)	9 (60%)	17 (52%)	19 (40%)	21 (24%)	14 (17%)	2 (4%)	82 (26%)
Dead (other cause)	26 (18%)	37 (21%)	1 (7%)	1 (3%)	1 (2%)	10 (12%)	25 (31%)	25 (50%)	63 (20%)
Dead (metastases)	76 (54%)	93 (54%)	5 (33%)	15 (45%)	28 (58%)	55 (65%)	43 (53%)	23 (46%)	169 (54%)
Total	*141*	*173*	*15*	33	48	86	81	50	314
20 yr follow up									
Alive	20 (21%)	22 (19%)	7 (64%)	7 (32%)	12 (35%)	8 (14%)	7 (13%)	1 (3%)	42 (20%)
Dead (other cause)	21 (22%)	29 (25%)	1 (9%)	1 (5%)	1 (3%)	10 (18%)	19 (34%)	18 (51%)	50 (23%)
Dead (metastases)	56 (58%)	66 (56%)	3 (27%)	14 (64%)	21 (62%)	38 (69%)	30 (54%)	16 (46%)	122 (57%)
Total	97	117	11	22	34	56	56	35	214

Duration of symptoms No correlation could be demonstrated between the duration of the symptoms and the corrected survival rate (Table XXI)

Blind eyes Patients with blind painful eye experienced a distinctly worse prognosis than did the rest of the material e g the corrected 10 year survival rate was 44 % for the patients with blind eyes compared with 55 % for the other patients After 10 years of follow-up the difference between the rates leveled off (Table XXII)

Location of the tumor Thirty-eight of the melanomas were located in the ciliary body 316 in the choroid The corrected survival rates of patients with ciliary body melanomas were clearly worse than those of the rest of the material (Table XXII) The difference was apparent through the whole follow-up period

Table XXII

Corrected survival rates (in per cent) of patients 1) with blind, painful eye, 2) with ciliary body melanomas and 3) with tumors which were observed before enucleation compared with respective other patients

Follow up time	Blind eyes	Others	Ciliary body	Others	Preoperatively observed	Others
3 years	70	84	74	81	75	81
5 years	55	68	53	66	62	65
10 years	44	55	42	53	53	52
15 years	44	47	36	47	48	46
20 years	46	42	33	46	47	32

TABLE XXIII

Corrected survival rates (in per cent) of patients with choroidal and ciliary body melanomas by cell type of the tumor

Follow-up time	Cell type		
	Spindle-cell	Mixed	Epithelioid-cell
3 years	89	80	63
5 years	69	66	53
10 years	59	52	47
15 years	52	47	38
20 years	46	42	42

The follow-up time was over 20 years in 214 cases Out of these 42 (20 %) were still alive, 122 (57 %) had died from metastases and 50 (23 %) from other causes Out of the 42 patients who were alive in the 20-year follow-up another 9 died from metastases later The longest time from enucleation to death from metastases was 30 years

Only slight differences were observable between the death rates from metastases (Table XVIII) or between the corrected survival rates in each age group (Table XX) However, young age groups (under 50) experienced a somewhat better prognosis than did the patients over 50 The difference was most marked in the 3-year rates but was also apparent in the 5-year and the 10-year rates After the 10 years follow-up the rates of the oldest age groups become unreliable, the rates are however, given in Tables XVIII and XX

Table XX

Corrected survival rates (in per cent) of patients with choroidal and ciliary body melanoms by age

	Age group						Total
	0—29	30—39	40—49	50—59	60—69	70—	
3 years	93	94	81	79	78	74	80
5 years	67	71	72	62	65	59	65
10 years	67	59	58	46	49	53	52
15 years	67	55	42	35	47	54	46
20 years	73	36	48	31	46	54	43

Table XXI

Crude and corrected survival rates (in per cent) of patients with choroidal and ciliary body melanomas by duration of symptoms

Follow-up time	Duration of symptoms							
	< 1 month		1—3 months		4—12 months		> 1 year	
	Crude	Corrected	Crude	Corrected	Crude	Corrected	Crude	Corrected
3 years	84	85	69	72	81	87	64	71
5 years	68	69	49	54	61	70	45	56
10 years	47	57	35	43	43	55	24	44
15 years	35	52	25	41	26	44	18	42
20 years	18	44	12	38	21	45	23	51

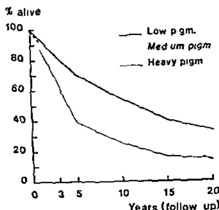


Fig 9

Crude survival rates of patients with choroidal and ciliary body melanomas in Finland in 1923—1966 by pigment content of the tumor cells

Size of the tumor Only a small difference was seen between the corrected survival rates of small and medium sized tumors (Table XXV) *Large tumors exhibited much lower survival rates*

Table XXV

Corrected survival rates (in per cent) of patients with choroidal and ciliary body melanomas by size of the tumor

Follow-up time	Size of the tumor		
	< 38 mm	38—74 mm	≧ 75 mm*
3 years	87	86	72
5 years	67	77	55
10 years	58	63	42
15 years	49	54	40
20 years	44	47	40

Extent of the tumor A good correlation was achieved between the extent of the tumor and prognosis of the patients The 10-year corrected survival rate of tumors without invasion was 71 % that of patients with a rupture of the Bruch s membrane 52 % in cases with invasion into the sclera 37 % and if extrabulbar *growth was noticed* only 12 % (Table XXVI Fig 10)

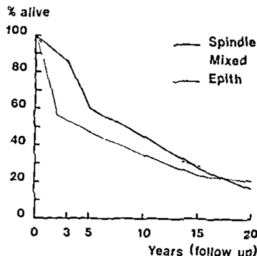


Fig 8
Crude survival rates of patients with choroidal and ciliary body melanomas in Finland in 1923—1966 by cell type of the tumor

Cell type Patients with melanomas of spindle-cell type had a better prognosis than those with melanomas of epithelioid-type cells (Table XXIII Fig 8) The prognosis of patients with tumors of mixed type fell between these two extremes

Pigment and reticulin content Low pigment content of melanoma cells proved to be a favorable prognostic sign the difference between the survival rates for tumors with medium pigment content and heavy pigment content was small (Tabl XXIV, Fig 9)

No correlation was observable between the reticulin content of the tumor tissue and prognosis of the patients (Table XXIV)

Table XXIV
Corrected survival rates (in per cent) of patients with choroidal and ciliary body melanomas by 1) pigment content of the tumor cells and 2) reticulin content of the tumor tissue

Follow-up time	Pigment content			Reticulin content		
	Low	Medium	Heavy	Low	Medium	Heavy
3 years	88	77	73	78	82	74
5 years	77	60	52	60	66	57
10 years	64	42	42	44	53	40
10 years	56	44	38	45	41	42
20 years	51	37	41	48	30	32

Table XXVII

Corrected survival rates (in per cent) of patients who were treated with X ray postoperatively compared with patients without X ray treatment

Follow up time	X-ray treatment	No X-ray treatment
3 years	85	77
5 years	68	64
10 years	52	52
15 years	43	50
20 years	36	52

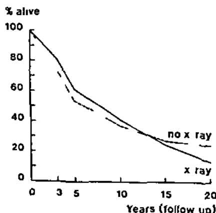


Fig 11

Crude survival rates of patients with choroidal and ciliary body melanomas in Finland in 1923—1966 in relation to postoperative x ray treatment

Effect of preoperative observation In 32 cases the enucleation was not performed immediately *instead* the eye was observed for some time in order to ascertain growth in the tumor The observation period was less than a month in 9 cases 1—3 months in 5 cases and over 3 months in 18 cases During the observation period growth was noticed in all tumors which subsequently led to enucleation No clear difference was observable in the survival rates between those patients who had a delayed enucleation and the rest of the material (Table XXII)

Enucleation refused Five patients who *refused* enucleation were included in this material Thus the diagnosis in these cases was not

Table XXVI

Corrected survival rates (in per cent) of patients with choroidal and ciliary body melanomas by extent of the tumor

Follow-up time	Extent of the tumor: No invasion	Ruptured Bruch's membrane	Invasion into the sclera	Extrabulbar growth
3 years	90	78	75	47
5 years	71	67	62	24
10 years	64	52	37	12
15 years	54	47	25	(13)[1]
20 years	42	47	29	(25)

[1] After six years of enucleation all 17 patients with extrabulbar growth were dead

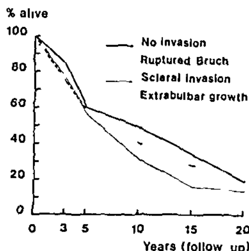


Fig 10

Crude survival rates of patients with choroidal and ciliary body melanomas in Finland in 1923—1966 by extent of the tumor (assessed histologically) at time of enucleation

Mode of treatment The correlation between the mode of treatment and prognosis was analyzed in two categories only operation without postoperative X-ray and operation followed by radiotherapy The 3-year and the 5-year corrected survival rates of patients who received postoperative radiotherapy was better than that of patients without X-ray (Table XXVII Fig 11) After 10 years of follow-up the reverse was true a better prognosis was encountered for patients to whom no radiotherapy was instituted

Table XXVII

rected survival rates (in per cent) of patients who were treated with X ray toperatively compared with patients without X ray treatment

llow up ne	X ray treatment	No X-ray treatment
years	85	77
years	68	64
years	52	52
years	43	50
years	36	52

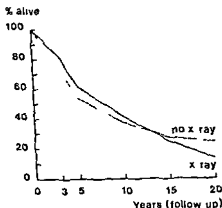


Fig 11
Crude survival rates of patients with choroidal and ciliary body melanomas in Finland in 1923—1966 in relation to postoperative x ray treatment

Effect of preoperative observation In 32 cases the enucleation was not performed immediately instead the eye was observed for some time in order to ascertain growth in the tumor The observation period was less than a month in 9 cases 1—3 months in 5 cases and over 3 months in 18 cases During the observation period growth was noticed in all tumors which subsequently led to enucleation No clear difference was observable in the survival rates between those patients who had a delayed enucleation and the rest of the material (Table XXII)

Enucleation refused Five patients who refused enucleation were included in this material Thus the diagnosis in these cases was not

histologically secured Four of these died from metastases after 2, 3, 14 and 15 years of follow-up One who died from other cause died one year after the initial examination

DISCUSSION

The crude survival rates are useful in the evaluation of the general fate of the patient material However, in studies on prognosis the survival rates are usually calculated by various break-downs of the material in order to assess the significance of various prognostic factors If the age distributions of the patients in the groups to be compared are not similar, crude survival rates lead to erroneous conclusions, because the expected survival rate is greatly dependent on the age of the patients Therefore, corrected survival rates have been calculated in this study In principle these rates correspond to the so-called relative survival rates, i e ratios of observed to expected rate Moreover, the assessment of the real cause of death of each individual as was done in this study should lead to even more correct estimate of the prognosis than use of relative survival rates which assumes that the expected survival of the patients group corresponds to that of the general population Serious shortcomings may however, arise in the application of the corrected survival rates as defined in this survey The figures are namely greatly influenced by the definition of the cause of death Even the dichotomy 'death from metastases from melanoma — other causes leads in many instances to serious problems, especially if one has to rely on old data and information of different sources (relatives, hospital records death certificates etc) On the other hand the same errors and disadvantages are operating in all patient groups which were compared in this study which makes the use of the corrected survival rates justified for comparisons

The survival of patients with melanoma of the choroid and ciliary body is determined by the relatively slow progression of the disease which means that the short-term prognosis is rather favorable while on the other hand deaths from metastases may occur decades after institution of the treatment Consequently no absolute cure can be expected for any individual patient (Chisholm 1953 Newton 1965)

In the present series the corrected survival rate which takes only those deaths into account which were caused by metastases of melanoma was 65 % after the 5 years and 51 % after the 10 years of follow-up On the 42 patients still alive after 20 years following the operation 9 died from metastases These figures are very close to

those reported by Jensen (1963) from Denmark In a large American series presented by Paul et al (1962) the corresponding 5-year and 10 year rates were 71 % and 60 % i e a little higher than those reported from Finland and Denmark However a relatively large proportion of patients was lost from the follow up in the material of Paul et al (1962) which makes the comparison of the results difficult The great differences in the reported survival rates can mostly be accounted for by methodological and other technical details losses from the follow-up, differences in the source and the age distribution of the patients differences in the definition of the cause of death etc (cf Lommatsch & Dietrich 1976) There seems to be no evidence that real differences exist in the prognosis of patients with melanoma of the choroid and ciliary body in the different parts of the world

The age and the sex of the patients as prognostic factors have been studied extensively but the results have been somewhat contradictory (Paul et al 1962 Jensen 1963 McLean et al 1977) In the present study the differences in the corrected survival rates in the different age groups were relatively small (Table XX) However the patients under 50 years of age experienced a better prognosis than the patients over 50 Other authors have observed greater differences between the age groups the prognosis has always been best among young patients (Westerveld—Brandon & Zeeman 1957 Paul et al 1962 Jensen 1963 Shammas & Blodi 1977) Due to the poor prognosis in old age Westerveld—Brandon & Zeeman (1957) concluded that there is no point in performing enucleation for patients over 60 years of age Results obtained in this study do not support this opinion

Prognosis of melanoma of the choroid and ciliary body showed no sex differences in Finland A similar result has been obtained by Jensen (1963) McLean et al (1977) and Shammas & Blodi (1977) Pregnant women have reported to experience a worse prognosis than other women (Frenkel & Klein 1966 Jensen 1970) None of the patients in the present series were known to be pregnant

Thirty two patients had been followed up for some time before enucleation Although growth was noticed in a number of these tumors this did not impair the prognosis of the patients A short preoperative observation period has been suggested by Zimmerman & McLean (1975) For of the 5 patients in the present series who refused operation died from metastases Hence there seems to be no reason to encourage a longer postponement of the treatment although absolute security of the benefits of the enucleation does not exist (Anderson & O Neil 1957 Zimmerman & McLean 1975)

Extrabulbar growth deep invasion into the sclera rupture of

the Bruch's membrane and growth inside the eye leading to blindness along with elevated intraocular tension with pain were prognostically unfavorable findings This means that expansive growth of the tumor is associated with worsening prognosis (Teraskeli 1928, Jensen 1963, Shammas & Blodi 1977) However, different opinions exist as to the importance of the observations concerning the Bruch s membrane According to Jensen (1963), the rupture is not a significant finding, whereas the opposite was concluded by Shammas & Blodi (1977)

Prognosis of patients with melanoma of the ciliary body proved worse than that of tumors in the choroid Due to the anterior location these tumors do not give symptoms at early stages of the disease and thus the diagnosis will perhaps be delayed On the other hand, ciliary body melanomas are in close connection with ciliary vessels and this anatomical relation as well as the constant movement of the ciliary muscle may facilitate the spread of tumor cells into the blood stream Contrary to the findings made in this study, Jensen (1963) did not find any differences in the prognosis between the ciliary body and the choroid melanomas McLean et al (1977) showed that the tumors in the anterior parts of the choroid had a worse prognosis than other tumors of the choroid, but rather surprisingly the tumors of the ciliary body had a better prognosis

Tumors composed predominantly of spindle cells had a better prognosis than the other tumor types although the differences in the survival rates were smaller than in some previous studies (Paul et al 1962, Jensen 1963, Shammas & Blodi 1977) Due to the uncertainties in the comparability of the groups defined by the cell type of the tumor, which were discussed on page 36 comparison of the absolute figures in different studies is useless

Increased melanin content of the tumor cells was shown to be associated with worse prognosis The same has been observed by other authors (Paul et al 1962, McLean at al 1977) On the other hand reticulin content of the tumor tissue was not of importance in assessing the prognosis of the patients Jensen (1963) came to the same conclusion Hence, the original observation by Callender and Wilder (1935) that heavy reticulin content carries a favorable prognosis has not been ascertained in later studies

In general the size of the tumor at the time of diagnosis has been shown to correlate with the prognosis the larger the tumor the worse the outcome for the patients (Flocks et al 1955 Jensen 1963 Shammas & Blodi 1977) The definition of the various size categories as well as the methods of measuring the size have varied in the different studies Hence direct comparisons between survival rates by

the size of the tumor are not justified In this study, three size categories were used but the prognosis of the small-tumor group was similar to that of the medium size tumor group It appears that in measuring the two largest diameters of the tumor on the microscopical slide and then multiplying these gives a good estimate of the size of the neoplasm For practical purposes the tumors should then be divided into two categories small and large The lower limit of the large tumors applied in the present study was of an area of 75 mm Definitions of the large and small groups is of course arbitrary, but 75 mm² could also be well used in future studies

In this material approximately one-half of the patients had been treated with X ray into the orbit after enucleation The 3-year and the 5 year corrected survival rates were better in the X-ray treated group the 10-year rates were similar but after the 15 and the 20 years of follow-up the irradiated group experienced a worse prognosis than those only enucleated In respect to the short-term prognosis the result was similar to that observed by S Vannas (1959) and Sobanski et al (1965) but the opposite situation in respect to the long term follow-up seems to be a new observation It is difficult to find rational explanations to this phenomenon

B MELANOMA OF THE IRIS

RESULTS

Epidemiology There were 19 iris melanomas in the present material compared to 359 tumors of the choroid and ciliary body hence 5 % of all uveal melanomas were located in the iris This means that, on the average one to two new cases of iris melanoma would be diagnosed annually in Finland

Fourteen of the patients (74 %) were females and only 5 were males The age distributions of the series is given in Table XXVIII The youngest patient was 14 and the oldest was 75 years old The mean age of the patients was 43 years

Clinical picture A pigmented spot on the iris had been observed since birth in 7 patients (37 %) and an additional two had noticed a spot at least ten years prior to the diagnosis of a melanoma (Table XXIX) Eight patients reported that they had noticed growth in the tumor all the time that they had been aware of it, and in five cases the growth had commenced later (Table XXIX)

the Bruch s membrane and growth inside the eye leading to blindness, along with elevated intraocular tension with pain were prognostically unfavorable findings This means that expansive growth of the tumor is associated with worsening prognosis (Teraskeli 1928, Jensen 1963, Shammas & Blodi 1977) However, different opinions exist as to the importance of the observations concerning the Bruch's membrane According to Jensen (1963), the rupture is not a significant finding, whereas the opposite was concluded by Shammas & Blodi (1977)

Prognosis of patients with melanoma of the ciliary body proved worse than that of tumors in the choroid Due to the anterior location, these tumors do not give symptoms at early stages of the disease, and thus the diagnosis will perhaps be delayed On the other hand, ciliary body melanomas are in close connection with ciliary vessels and this anatomical relation as well as the constant movement of the ciliary muscle may facilitate the spread of tumor cells into the blood stream Contrary to the findings made in this study, Jensen (1963) did not find any differences in the prognosis between the ciliary body and the choroid melanomas McLean et al (1977) showed that the tumors in the anterior parts of the choroid had a worse prognosis than other tumors of the choroid but rather surprisingly, the tumors of the ciliary body had a better prognosis

Tumors composed predominantly of spindle cells had a better prognosis than the other tumor types although the differences in the survival rates were smaller than in some previous studies (Paul et al 1962, Jensen 1963 Shammas & Blodi 1977) Due to the uncertainties in the comparability of the groups defined by the cell type of the tumor, which were discussed on page 36 comparison of the absolute figures in different studies is useless

Increased melanin content of the tumor cells was shown to be associated with worse prognosis The same has been observed by other authors (Paul et al 1962, McLean at al 1977) On the other hand, reticulin content of the tumor tissue was not of importance in assessing the prognosis of the patients Jensen (1963) came to the same conclusion Hence, the original observation by Callender and Wilder (1935) that heavy reticulin content carries a favorable prognosis has not been ascertained in later studies

In general, the size of the tumor at the time of diagnosis has been shown to correlate with the prognosis the larger the tumor, the worse the outcome for the patients (Flocks et al 1955 Jensen 1963 Shammas & Blodi 1977) The definition of the various size categories as well as the methods of measuring the size have varied in the different studies Hence direct comparisons between survival rates by

the size of the tumor are not justified In this study three size categories were used but the prognosis of the small-tumor group was similar to that of the medium size tumor group It appears that in measuring the two largest diameters of the tumor on the microscopical slide and then multiplying these gives a good estimate of the size of the neoplasm For practical purposes the tumors should then be divided into two categories small and large The lower limit of the large tumors applied in the present study was of an area of 75 mm² Definitions of the large and small groups is of course arbitrary but 75 mm² could also be well used in future studies

In this material approximately one-half of the patients had been treated with X ray into the orbit after enucleation The 3-year and the 5 year corrected survival rates were better in the X-ray treated group the 10 year rates were similar but after the 15 and the 20 years of follow up the irradiated group experienced a worse prognosis than those only enucleated In respect to the short-term prognosis the result was similar to that observed by S Vannas (1959) and Sobanski et al (1965) but the opposite situation in respect to the long term follow-up seems to be a new observation It is difficult to find rational explanations to this phenomenon

B MELANOMA OF THE IRIS

RESULTS

Epidemiology There were 19 iris melanomas in the present material compared to 359 tumors of the choroid and ciliary body hence 5 % of all uveal melanomas were located in the iris This means that, on the average one to two new cases of iris melanoma would be diagnosed annually in Finland

Fourteen of the patients (74 %) were females and only 5 were males The age distributions of the series is given in Table XXVIII The youngest patient was 14 and the oldest was 75 years old The mean age of the patients was 43 years

Clinical picture A pigmented spot on the iris had been observed since birth in 7 patients (37 %) and an additional two had noticed a spot at least ten years prior to the diagnosis of a melanoma (Table XXIX) Eight patients reported that they had noticed growth in the tumor all the time that they had been aware of it, and in five cases the growth had commenced later (Table XXIX)

Table XXVIII

Distribution of patients with iris melanoma by age and sex

Age	Males	Females	Total
—29	3	3	6
30—39	1	1	2
40—49		3	3
50—59	1	3	4
60—69		2	2
70—		2	2
Total	5	14	19

Table XXIX

Detection time and growth of iris melanomas

Tumor noticed	Growth all time	Growth later	No growth	No information	Total
Since birth	1	3	3	—	7
> 10 years	1	1	—	—	2
1—10 years	3	1	—	—	4
1—12 months	3	—	—	—	3
< 1 month	—	—	2	—	2
No information	—	—	—	1	1
Total	8	5	5	1	19

A tumor was noticed as a first symptom by 14 patients All these patients had a normal visual acuity at the examination and the irises showed no other abnormality than the tumor Four patients had a decreased visual acuity Elevated intraocular tension was observed in all these four, the lens was opaque in two and a hyphaema was seen in one The visual aquity of one patient was unknown

In defining the location of the tumor, the iris was divided into nasal superior, temporal and inferior quadrants The inferior quadrant was the location of 12 melanomas (63 %)

Three tumors were located in the middle of the iris two at the pupillary border and 12 extended from near the pupillary border to the chamber angle One melanoma spread diffusely in patches over the whole iris

Treatment Iridectomy or iridectomy-cyclectomy was performed

in 11 cases The eye with a melanoma was enucleated in 6 cases one of them with a previous iridectomy in four of these cases the intra-ocular tension was high and in another two the melanoma had grown far over the angle into the ciliary body Three patients refused the operation

Histopathology Tumor tissue was obtained for reclassification in ten cases Seven melanomas were of the predominantly spindle-cell type two were of the mixed cell type and in one case it was not possible to determine the cell type

Prognosis The follow up time was at least 10 years in all 19 cases at least 15 years in 14 cases and 20 or more years in 6 cases During the follow up time two patients died from metastases one (survival time 5 year) had a diffuse tumor of the iris the other (survival time 10 years) had high intraocular tension and a tumor which had spread out into the ciliary body The histological specimens of these two cases were not available

Out of the three cases who refused the operation none have so far died of metastases Two of them have already survived more than 20 years and the third patient died one year after examination from a cause unrelated to the tumor

DISCUSSION

In many respects melanoma of the iris is different from that of the choroid and ciliary body The risk of contracting iris melanoma is much lower the patients are younger a greater proportion of the tumors are of spindle-cell type and the prognosis of the patients is much more favorable

The proportion of iris melanomas among all melanomas of the uvea has shown wide variations in earlier reports A ratio of 1 6 was noticed by Holland (1967) and a figure as low as 1 30 was presented by Jensen (1963) The ratio observed in the present material 1 19 and that given by Rones & Zimmerman (1958) 1 15 fall between these two extremes

The sex ratio of the patients with iris melanoma has also varied considerably which is at least partly due to the small number of cases A female preponderance was reported by Ashton (1964) and Duke & Dunn (1958) but the reverse was true in the material of Rones & Zimmerman (1958) In the present material up to 74 % of the patients were females

The mean age of patients with iris melanoma in earlier reports

has ranged from 37 to 48 years (Jensen 1963, Ashton 1964, Duke & Dunn 1958, Rones & Zimmerman 1958) In general, patients with an iris melanoma have been 10—20 years younger than those with a melanoma of the choroid and ciliary body (Rones & Zimmerman 1958, Cleasby 1958) In the present material the mean age of patients with a melanoma of the choroid and ciliary body was 55 years which is 12 years higher than that of the patients with an iris melanoma, 43 years Melanoma of the iris can be found in both the old and the young individuals Three patients out of 105 were under the age of 10 in the material of Ashton (1964)

The proportion of patients in which a pigmented spot had been noticed since birth of for at least 10 years prior to the diagnosis of a melanoma was high (47 %) as compared to the figures in some of the other reports (Duke & Dunn 1958, Jensen 1963) It has been generally recognized that melanoma of the iris starts to develop from a pre-existing nevus If the iris is heavily pigmented, it may be difficult to notice a small brownish nevus before it starts growing and already presents as a melanoma The irises of the Finns are light, which may explain why the patients so often had noticed a spot in the iris

A peculiar finding in this survey was the predilection of the inferior quadrant of the iris as the location of a melanoma This has been reported earlier (Cleasby 1958, Rones & Zimmerman 1958 Jensen 1963), but no hypotheses have been introduced as concerning to the cause of this uneven anatomical distribution

The spindle-cell type melanoma is more common among iris melanomas than among other melanomas of the uvea (Rones & Zimmerman 1958, Jensen 1963 Ashton 1964) The observation made in this study agrees with earlier findings (7 spindle-cell tumors out of 10) although the number of cases is very small Epithelioid-cell type melanomas are rarities among the iris melanomas but cases have been reported (Ashton 1964, Heath 1964) The cytological classification of melanomas of the iris is rather difficult compared to other uveal melanomas

In accordance with the findings of the cell type of iris melanomas the prognosis of the patients is very favorable and clearly better than that of melanomas of the choroid and of the ciliary body None of the 101 cases followed-up in the series of Ashton (1964) died from metastases during the follow-up period of 5—20 years Rones & Zimmerman (1958) followed all but 6 of their 125 cases only three died from metastases Fenske & Burr (1964) have reported a lethal iris melanoma in a child

Two deaths from metastases among the 19 patients in the present

series is a rather high frequency In both these cases the tumor had presented as many separate focuses over the iris A similar melanoma of the iris has been described by Martin (1973) The other tumor had grown into the ciliary body Growth into the ciliary body was apparent also in those cases of *Jensen (1963)* who died of their melanomas A conclusion can be drawn that melanoma of the iris has a very favorable prognosis provided that the tumor has remained localized

None of the three patients of the present series who refused operation died from metastases of the melanoma Two explanations for this can be given one that the melanoma of the iris is so benign that no operation is necessary unless growth of the tumor is encountered, two that the tumors which had been diagnosed on the basis of clinical examination only in fact represented some benign lesions presumably nevi Anyhow this implies that observation *without operative intervention may in certain cases* be warranted and if operation will be instituted local excision of the tumor should be considered and only in cases with tumors spread into the ciliary body should enucleation be made

V CONCLUSIONS

On the basis of the results of the present study and comparisons with observations made elsewhere, the following conclusions have been drawn

1) Melanoma of the uvea is a rare disease in Finland, only some 25 new cases being diagnosed annually The risk of uveal melanoma in Finland is similar to that in other Nordic countries but higher than in colored populations Hence the very low pigmentation of the eyes of the Finns does not mean that the incidence of uveal melanoma in Finland would be exceptionally high

2) The risk of uveal melanoma has not changed in Finland during 1953—1973 This indicates that the risk factors of uveal melanoma have remained constant in spite of the marked changes which have taken place in the environment and habits

3) Melanoma of the uvea is only exceptionally diagnosed in childhood The risk increases with age, and is highest among old individuals On the average, patients with melanoma of the iris are 10—15 years younger than those with melanoma of the choroid and ciliary body

4) A majority (85 %) of the melanomas of the uvea are located in the choroid About 10 % of the tumors are found in the ciliary body and only 5 % in the iris This anatomical distribution corresponds to that reported from other countries and indicates that the irises of the Finns, in spite of the low pigment content do not carry an excessive relative risk of melanoma

5) As can be expected on the basis of the growth characteristics of the melanomas of the choroid and ciliary body, two thirds of the patients complain of decreased visual acuity as their first symptom Iris melanomas are nearly always preceded by a pigmented spot noticed by the patient and/or his or her relatives Due to the lightness of the irises of the Finns the melanomas, and nevi preceding them will be diagnosed in Finland earlier than in countries where people have darker eyes and many patients are aware of the growth of their tumors

6) Histological classification of uveal melanomas by cell type into three categories (predominantly spindle predominantly *epithelioid*, and mixed) can be recommended for assessing of the prognosis of a given patient in routine work tumors of predominantly spindle-cell type having a better prognosis than the two other groups Other findings suggesting prognosis better than the average are low pigment content of the tumor cells small size of the tumor and location of the tumor in the iris Rupture of the Bruch s membrane invasion of the tumor deep into the sclera and especially extrabulbar growth are unfavorable findings in terms of the prognosis of the patient Other unfavorable prognostic signs are location of the melanoma in the ciliary body old age of the patient and blindness and pain in the affected eye

7) Enucleation is the treatment of choice in cases with undoubtful diagnosis of choroid or ciliary body melanoma If uncertainty of the diagnosis exists observation of the patient with repeated examinations using all available methods is justified in order to avoid unnecessary enucleation. A much more conservative approach is recommended for melanomas of the iris where observation of the patient is to be considered provided that no growth of the tumor is observable Even then an *iridectomy or iridocyclectomy is to be per*formed and enucleation seems to be necessary in those cases only in which the tumor extends to the ciliary body or covers a large part of the iris with diffuse growth or multiple foci Postoperative radiotherapy into the orbit dies not improve the long-term prognosis of the patients

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Two-thirds of the patients with choroidal and ciliary body melanomas complained of decreased visual acuity as their first symptom Pain was the next in rank order (24 %) The duration of the symptoms was more than one year in 20 % of the patients On the other hand a duration of less than one month was given by 23 % of the patients Inflammatory signs were observable in 14 % of the patients with melanoma of the choroid as compared to 31 % in eyes with ciliary body tumor An elevated intraocular tension was measured in 27 % of the patients

Ninety-one eyes were classified into the category blind painful eye The mean age of the patients in this group was 62 4 years i e clearly higher than that for the total series

A histological specimen was obtained for reclassification in 233 melanomas of the choroid and ciliary body Six per cent of the choroidal tumors were located in the anterior part of the bulbus The tumors were classified by cell type into the following three categories predominantly spindle-cell type predominantly epithelioid-cell type and mixed type Tumors composed of predominantly spindle cells constituted 38 % of all melanomas of the choroid and ciliary body 19 % were of the predominantly epithelioid-cell type and 44 % were of the mixed type Patients with epithelioid cell type tumors were older than those with the other types

The pigment content of the tumor cells was estimated to be low in 42 % of the cases medium in 28 % and heavy in 30 % The pigment content was associated with tumor type the spindle-cell type tumors contained less pigment than the epithelioid cell type tumors On the other hand tumors composed of epithelioid-type cells contained less reticulin than the other groups In the age groups over 60 there were more large tumors than among the younger patients

No invasion was observed in 35 % of the tumors The Bruch s membrane was ruptured in 50 % of the eyes while deep scleral invasion and extrabulbar growth were encountered only in 7 % and 8 % of the eyes respectively

The short term prognosis of the patients with melanoma of the choroid and ciliary body was rather favorable Roughly 50 % of the patients died from metastases during the follow up of the 10 years However deaths from metastases occurred even after long follow-up periods the longest interval between enucleation and death from metastases was 30 years

No difference was observable in the prognosis between males and females Patients under 50 years of age experienced somewhat better prognosis than older patients The following findings showed to be

VI SUMMARY

The aim of this study was to analyze the epidemiology clinical features, histology, and prognosis of uveal melanoma in Finland Throughout the study, an attempt was made to correlate the observations with the fact that the pigmentation of the Finns is exceptionally low

To assess the incidence of uveal melanoma in Finland all melanomas of the eye reported to the Finnish Cancer Registry in 1953—1973, a total of 548 cases, were analyzed The anatomical distribution of the tumors from 1972—1973 was further elucidated The mean annual crude incidence rate of uveal melanoma was estimated as 0 5/100,000 person-years No change with time in the risk of uveal melanoma was observable during the study period

The clinical material 378 cases was collected from all eye clinics and hospitals with eye departments in Finland the series covered the years 1923—1966 It was estimated that this material represented about 2/3 of all the cases diagnosed in the country during the time in question The location of the tumor was the choroid in 321 cases (85 %) the ciliary body in 38 cases (10 %) and the iris in 19 cases (5 %) Melanomas of the choriod and ciliary body and those of the iris were analyzed separately

On the basis of the incidence figure obtained from the Cancer Registry material and the sex and age distribution of the clinical material it was concluded that no differences existed in the risk of melanoma of the choroid and ciliary body between males and females The mean annual number of new cases of melanoma of the choroid was estimated as 22—23 and that of melanomas of the ciliary body as 2—3 The incidence was very low in age group under 30 The incidence increased with age and was highest 2 1/100,00 person years in the age group of 70 years and over The m[illegible] ge of patients with melanoma of the choroid [illegible] iary body [illegible] ars for males and 56 years for females

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No difference was observable in the prognosis between males and females Patients under 50 years of age experienced somewhat better prognosis than older patients The following findings showed to be

favorable in terms of the prognosis of the patient spindle-cell type of the tumor, low pigment content of the melanoma cells, and small size of the tumor Rupture of the Bruch s membrane invasion of the tumor cells deep into the sclera, and extrabulbar growth of the tumor were unfavorable signs Patients with a blind, painful eye experienced a worse prognosis than other patients Tumors in the choroid carried a better prognosis than the ciliary body melanomas Postoperative X-ray treatment into the orbit gave higher survival rates after the 3 and the 5 years of follow-up as compared to enucleation only, but after 10 years, the rates tended to be lower than for patients without X-ray

Nineteen melanomas (5 %) were located in the iris Patients with iris melanoma were younger than those with choroidal and ciliary body melanomas (mean ages 43 and 55 years) A pigmented spot in the iris had been observed since birth or for at least 10 years prior to the diagnosis by 9 patients, and 13 patients had observed growth in the tumor The proportion of tumors composed of predominantly spindle cells was higher than that for melanomas of the choroid and ciliary body Only two patients died from metastases In one of these the melanoma had spread into the ciliary body, in the other it presented as a diffuse tumor with multiple focuses over the iris

On the basis of the results obtained in this study and comparisons with other reports it was concluded that the risk of Finns to contract uveal melanoma is the same as in the other Nordic countries and higher than in darker populations No excess risk could be accounted for by the low pigmentation and light irises of the population in Finland The unchanged risk suggests that the risk factors responsible of inducing uveal melanomas have not changed with changing environment and habits

The clinical features, histological findings and prognosis of uveal melanoma in Finland largely correspond to those reported from other countries However due to the light color of the irises the iris melanomas in Finns will be noticed earlier than in darker races and many patients are aware of the growth of their tumors in some instances for a long period of time Apart from this it was concluded that the light complexion of the Finnish population does not exert any major influence upon the biological and other characteristics of uveal melanoma in Finland

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Kauniainen June 1977

Ilkka Raivio

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SUPPLEMENTUM 132

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Studies on Computerized Perimetry

by

Anders Heijl

SCRIPTOR COPENHAGEN 1977

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University of Lund Lund Sweden

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The present thesis is based on the following publications

A An automatic static perimeter design and pilot study (in collaboration with C E T Krakau)
Acta ophthal (Kbh) 53 293 310 1975

B An automatic perimeter for glaucoma visual field screening and control Construction and clinical cases (in collaboration with C E T Krakau)
Albrecht v Graefes Arch Ophthal 197 13 23 1975

C Automatic perimetry in glaucoma visual field screening A clinical study
Albrecht v Graefes Arch Ophthal 200 21 37 1976

D Time changes of contrast thresholds during automatic perimetry
Acta ophthal (Kbh) 55 1977 In press

E Computer test logics for automatic perimetry
Acta Ophthal (Kbh) 55 1977 In press

F A note on fixation during perimetry (in collaboration with C E T Krakau)
Acta ophthal (Kbh) 55 1977 In press

In the following presentation these papers will be referred to as marked above

CONTENTS

The field of vision is that portion of space in which objects are visible at the same moment during steady fixation of the gaze in one direction (Traquair 1942) Large and bright objects can be seen in the periphery of the visual field small and/or faint targets can only be seen if they are placed closer to the axis of vision Pathological changes in the visual field may occur as the result of many diseases in the eye itself or in the central nervous system

The recording of visual fields perimetry is an important often crucial examination method in ophthalmology It was introduced as a clinical method by von Graefe (1856) who used a black board on which the test objects were moved and by Foerster (1869) who constructed a special apparatus for visual field examination a perimeter consisting of an arc surrounding the eye to be examined At that time the clinical visual field examination was carried out with only one test object A more detailed picture of the visual field is obtained by using several different test objects as shown by Bjerrum (1889) This is now a routine method Most often perimetry is performed with moving stimuli kinetic perimetry but visual field examination by means of fixed stimuli static perimetry as introduced by Sloan (1939) is now being used more and more

Traditionally perimetry has been manually performed by an examiner a perimetrist Manual perimetry is exacting and time consuming It involves a great deal of subjectivity not only on the part of patient but also on that of the perimetrist and the risk of erroneous results most often visual field defects which go undetected is considerable Also it has often been affirmed that the routine visual field records forming the basi for the therapeutic measures taken by clinicians are frequently of inferior quality This is not due to bad tools but rather to lack of time and sometimes understanding on the part of the perimetrist

Under these circumstances it is natural that there should be a demand

for perimeters designed to shorten visual field examination or visual field screening and possibly to make routine perimetry more reliable During the fifties and sixties several such semi-automatic devices were introduced, e g the Harrington-Flocks visual field screener (Harrington & Flocks 1954), the Fincham-Sutcliffe screening scotometer (Sutcliffe 1963), the Globuc device (Buchanan & Gloster 1965), and the Friedmann visual field analyzer (Friedmann 1966) Some of them have come to be fairly widely used, which proves the need for such instruments Later commercially available fully automatic perimeters followed (Ocutron Automatic Electronic Perimeter Biotronics Autofield I) However, the testing made possible by these perimeters is still fairly simple, since it involves an examination conducted with only one stimulus intensity and no advanced strategy Unfortunately no clinical studies have been published in which these instruments are used

The very fast development of electronics during the last decade has made it not only possible but also natural to design an electronically controlled perimeter employing a relatively intricate test procedure a computerized perimeter Two papers dealing with theoretical aspects of computerized perimetry were published in 1972 (Fankhauser et al 1972 Koch et al 1972), but when the present investigations started no descriptions of computerized perimeters had been published nor were any studies available involving the use of such devices

The primary aim of the present studies was to analyse the prerequisites for fully automatic computerized perimetry in order to find out whether such a procedure was feasible and how it should be carried out For this purpose a computerized perimeter and various test logics were to be designed and tested in practical experiments on patients

When the investigations started there were many unsolved but fundamental que tions closely connected with the behaviour of the patient in an impersonal testing system like an automatic perimeter could one expect the average patient to work for himself in such an apparatus without the continuous encouragement of a perimetrist? Would he become less attentive after some time and give unreliable answer ? How could one know if the patient maintained correct fixation? Were there modes of t st objects presentation less likely to provoke erroneous an wers than others?

In order to answer some of these questions a fairly simple prototype of an automatic perimeter was constructed and various testing conditions were tried out with this machine

Perimeter sy tem

Perimeter

A piece of board painted matt white was mounted on the arc of a Maggiore perimeter The board was evenly illuminated Fourteen light emitting diodes (LEDs) of yellow emission were mounted in holders on the back of the board along a meridian at 2 5^0 5^0 10^0 13 3^0 16 7^0 20^0 and 25^0 from a fifteenth red LED serving as fixation light LEDs are easily modulated up to very high frequencies The spectral distribution of the emitted light is constant on different intensity levels The l g^t rom the diodes was projected through small plexiglass light leaders which were fixed in 2 mm holes in the board The LEDs served as light sources for the test stimuli and as the board could be rotated fourteen central points along any meridian could be tested

These fourteen board mounted LEDs could be exposed on fifteen intensity levels numbered from 1 (the strongest) to 15 (the wakest) The ratio between two consecutive levels was 1 $\sqrt{2}$

A freely movable light spot of a fixed high intensity level could be projected onto the board of the perimeter This spot was so adju ted as to fall in the blind spot area of the eye to be tested and it was

for perimeters designed to shorten visual field examination or visual field screening and possibly to make routine perimetry more reliable During the 'fifties and 'sixties several such semi-automatic devices were introduced e g the Harrington-Flocks visual field screener (Harrington & Flocks 1954) the Fincham-Sutcliffe screening scoto meter (Sutcliffe 1963), the Globuc device (Buchanan & Gloster 1965), and the Friedmann visual field analyzer (Friedmann 1966) Some of them have come to be fairly widely used, which proves the need for such instruments Later, commercially available fully automatic perimeters followed (Ocutron Automatic Electronic Perimeter Biotronics Autofield I) However the testing made possible by these perimeters is still fairly simple since it involves an examination conducted with only one stimulus intensity and no advanced strategy Unfortunately no clinical studies have been published in which these instruments are used

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Test programmes were rapidly fed into the computer from an optical tape reader (Fig 1)

Test logic

A fundamental principle of the test logics for this perimeter and for almo t all perimetric test logics used later is a staircase mode of testing where the response to a certain stimulus determines the inten sity level to be used at the next stimulus presentation at the same point (compare Fig 2) Thus if a test point was lit at an intensity level i and the test subject pressed the appropriate button indicating that he had seen the stimulu the intensity level would be on a one step fainter level called i+1 the next time this point was tested On the other hand if no answer was given or the wrong button was pressed the intensity of this point would be on a one step stronger level

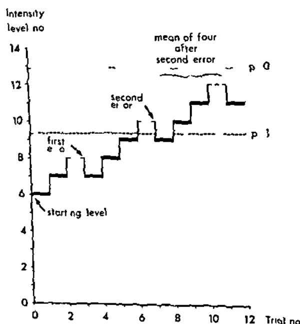


Fig 2 Example of test procedure at one single test point Stimulus level nu ber increases i e stimulus intensity is reduced with every correct interpreta tion (thick horizontal lines) and decreases with every false answer or when no answer is given (broken horizontal lines) p denotes probability of seeing (mere blunders not taken into consideration)

intended to serve as a device for fixation control

Computer system

The perimeter was connected to a minicomputer via a specially designed interface (Fig 1) The computer was programmed in the Extended Basic data language and the stimuli of the perimeter were lit on orders given in the test programme of the computer by means of Call statements This order, the output word of the computer, was translated by the interface into a current of 0 5 s duration at a specific level to a specific LED in the perimeter thus giving a test stimulus of a certain intensity in a certain location The test subject responded to a perceived stimulus by pressing one of two buttons (left if the stimulus was seen to the left of the fixation light right if it was seen to the right) This answer was translated by the visual field interface into an input word to the computer and a new stimulus was presented 0 5 s later If no answer was given within 2 0 s another input word meaning no reply', was sent to the computer

At the end of the test session the results were presented on a teletype numerically and as a tabulated curve

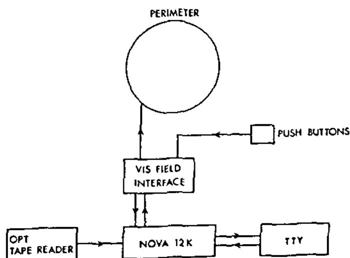


Fig 1 Block diagram of perimeter system

Test programmes were rapidly fed into the computer from an optical tape reader (Fig 1)

Test logics

A fundamental principle of the test logics for this perimeter and for almost all perimetric te t logics used later is a staircase mode of testing where the response to a certain stimulus determines the intensity level to be used at the next stimulus presentation at the same point (compare Fig 2) Thus if a test point was lit at an intensity level i and the test subject pressed the appropriate button indicating that he had seen the stimulus the intensity level would be on a one step fainter level called i+1 the next time this point was tested On the other hand if no answer was given or the wrong button was pressed the intensity of this point would be on a one step stronger level

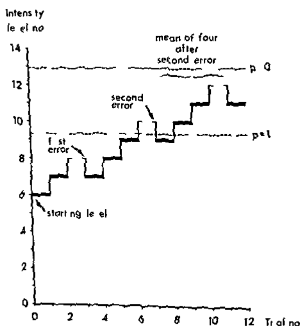


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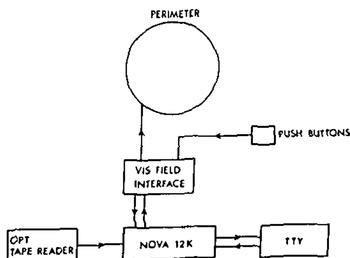


Fig 1 Block diagram of perimeter system

1) One test logic (the non random programme) was identical with the standard programme except for the fact that each test point was tested until its final value had been reached Thus the points were tested in an ordered sequence starting with the most central and ending with the most peripheral points

2) The ystem with two push buttons for the subject s answers used in this perimeter had previously been employed in other automatic devices developed at the Department of Experimental Ophthalmology in Lund e g in an apparatus for time series analysis of visual acuity (Krakau 1967) and in a device for automatic continuou recording of stereoscopic visual acuity (Krakau 1969/1970) In one of the test logics of the present study (the one button logic) only one push button was used instead of the two button system of the standard test logic Thus the patient did not have to give different responses to test stimuli to the left or to the right but pressed one and the same button meaning light perceived each time a stimulus was seen In all other respects this logic was identical to the standard logic

3) In the standard test logic the stimulus intensity decreased in a stepwise fashion as long as the patient answered correctly and the first stimulus which was not followed by a correct answer closed the testing of that specific test point However the patient may respond fal ely e g not pressing a button when seeing a light etc (Fig 2 first error) In one test logic (the second error programme) the threshold was determined the second time the subject did not respond correctly to an exposed stimulus The test proceeded to the point marked second error in Fig 2 one false negative answer was thus tolerated

4) If the test process is allowed to continue and no mistakes are made by the patient the stimulus intensity being reduced with every correct interpretation and increased with every false answer or when no answer is given the test process will finally be framed by the intensity levels where the probability of seeing is 1 and 0 (Fig 2) I will behave as a Markov process (random walk) with reflecting barriers (compare Krakau 1969) If the assumption is made that the probabilities of seeing for the different intensity levels remain constant during the test (an assumption which has shown to have a limited validity (D))

i-1, at the next trial The test process at each test point thus moved in a positive or a negative direction If no mistakes were made by the subject a change of sign in the movement of the test process meant that the test procedure was in or had just passed the threshold zone (in which the probability-of-seeing is greater than 0 but smaller than 1) The stimulus intensity had become either too faint to be perceived any more (correct answer ⟶ no answer) or finally strong enough to be perceived (no answer ⟶ correct answer)

Several different test logics were investigated A standard test programme serving as reference for the other test logics was constructed It had the following specifications

a) The stimuli appeared at random locations The stimulus to be shown was chosen by a random generator in the computer

b) At most test points the stimulus intensities were supraliminal at the beginning of the test

c) If the test subject had initially seen a stimulus in a certain position once or more the starting level being supraliminal and later did not correctly interpret a given (fainter) stimulus in the same position this point was not further tested If the stimulus was not seen initially its intensity increased by one step at each presentation until the appropriate button was pressed or until no answer was obtained at presentation of the maximum intensity level of the perimeter In both cases from the supraliminal or from the subliminal side the last perceived level in the test process was taken as the threshold level Thus normally the stimulus intensity would decrease in a stepwise fashion until the patient did not answer correctly on the presentation of the stimulus

d) The light spot projected onto the blind spot area was exposed at random intervals It was programmed to be shown on an average 1/16 of the total number of stimulus presentations The number of answers to this stimulus were stored by the computer Obviously if the test subject maintained correct fixation this stimulus could not be seen

Several modifications of this standard test logic were made

1) One test logic (the non random programme) was identical with the standard programme ex ept for the fact that each test point was tested until its final value had been reached Thus the points were tested in an ordered sequence starting with the most central and ending with the most peripheral points

2) The system with two push buttons for the subject s answers used in this perimeter had previously been employed in other automatic devices developed at the Department of Experimental Ophthalmology in Lund e g in an apparatus for time series analysis of vi ual acuity (Krakau 1967) and in a device for automatic continuous recording of stereoscopic visual acuity (Krakau 1969/1970) In one of the test logics of the present study (the one button logic) only one push button was used instead of the two button system of the standard test logic Thus the patient did not have to give different responses to test stimuli to the left or to the right but pressed one and the same button meaning light perceived each time a stimulus was seen In all other respects this logic was identical to the standard logic

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the mean of the intensity levels visited will approach a fixed value If such a mean is used as the measured threshold a decreased variation of these thresholds should be obtained One test logic using this principle (the mean of four logic) was constructed the mean of four intensity levels *visited after the second not perceived stimulus which* ended the test process in the second error' logic was calculated and used as threshold (Fig 2)

Experiment and material

The perimeter and the test logics were tested on eight normal eyes in repeated measurements The tests were fully automatic The test subjects were instructed to gaze steadily at the red fixation light of the perimeter during the whole test and to press the appropriate push button when perceiving a stimulus

Results and discussion

1) The fundamental result was that fully automatic perimetry was feasible Most people readily understood the rules at testing and managed in the impersonal test situation without the attention and encouragement of a perimetrist

2) The fairly large standard deviation of the results of the simple standard test logic was reduced by applying the more complicated test logics the second error and especially the mean of four logic (Fig 3) *though at the cost of an increased duration* of the test Thus in four out of five cases the second error logic yielded less variation than the standard programme and the reproducibility of the thresholds measured by the mean of four logic was better than that of the standard test logic in all six cases in whom both these logics were used

3) When the non random logic was used there was a tendency for the subject not to maintain fixation an increased frequency of answers to blind spot stimulus presentations was observed Thus a test logic using stimuli exposed in random order seemed to be better than a logic showing them in an orderly fashion at least when the described system for fixation control was used

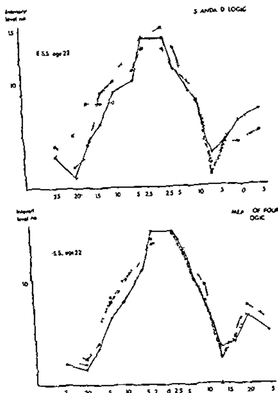


Fig 3 Five profiles across the horizontal meridian of the right eye The varia tion of the test results was smaller with the mean of four logic than with the standard logic

4) If a test subject gives answers when not seeing a stimulus the effect could be expected to be more harmful with a one button logic in which every false positive answer is interpreted as a correct answer than with a two choice logic in which the probability of such a false answer to be recognized as correct is 0 5 In the present study the dispersion of the test results was found to be smaller when only one button was used (the one button logic) than when the standard programme with two buttons was applied This indicates that no large number of such false positive answers was produced This impression was further confirmed by the fact that the number of answers to blind spot

stimulus presentations was similar when the two test logics were used It seemed likely that instead of being a desirable control mechanism the two-choice system put an increased strain on the subjects thus affecting the results in a negative way

5) The test subjects often reported that after about 5 min of te ting they had a feeling that the background luminosity had changed, and that sudden small light flashes and other irritating optic phenomena occurred There was an impression that impairment of the test subjects achievements might have taken place after a while, though this was ne ver actually measured It was felt to be an advantage if the test ses sions could be kept short It was decided to investigate the influence of test time on threshold and fixation

AN AUTOMATIC PERIMETER FOR GLAUCOMA VISUAL FIELD SCREENING AND CONTROL CONSTRUCTION AND CLINICAL CASES (B)

Experiments with the simple prototype were promising A clinically more serviceable perimeter was to be constructed LEDs had proved to be suitable as light sources, they were easily exposed over a wide intensity range without the use of mechanical arrangement like relay-controlled neutral grey filters The application of fixed stimuli also made complicated and sensitive devices for the projection of stimuli unnecessary Stimulus position could be momentarily changed and the perimeter could be operated in complete silence

Certainly the use of fixed stimulus positions implies a limitation in the number of positions in the visual field that can be examined but even with a perimeter allowing any point in the visual field to be tes ted the number of points investigated must be limited since the exa mination time must be kept reasonably short

Mechanical problems are thus largely avoided in a perimeter employing fixed LEDs as stimuli and it is easier to build such a perimeter than an automatic projection perimeter like that described by Spahr (1973) It was therefore decided to continue to use LEDs as light sources in a new computerized perimeter

Perimeter system

Most patients who undergo visual field examinations belong to the groups glaucoma or glaucoma suspects Current opinion on early visual field defects in glaucoma is based mainly on the work of Aulhorn and Harm (Aulhorn & Harms 1967 Aulhorn 1969) When recognizable these defects are mall circumscribed deep scotomata which may appear anywhere in the central visual field typically in the Bjerrum area between 2^0 and 18^0 of eccentricity Armaly has developed a screening method a selective perimetry for glaucoma cases in which most of the test is performed statically with supraluminal stimuli at points from 5^0 to 15^0 of eccentricity (Armaly 1972) This test has been widely adopted and has proved useful (Rock et al 1973 Krieglstein & Andrae 1975) These facts were utilized when the stimulus pattern of the new perimeter was designed as the perimeter was intended to be used primarily for glaucoma visual field screening and control The test points were concentrated in the central visual field (5^0 - 25^0) (Fig 5) No te t points were placed in the peripheral parts of the visual field in agreement with Blum et al (1959) who claim that the peripheral parts of the visual field are of minor intere t

64 LEDs were mounted in holes in a black PVC board the front of which wa covered by a thin semi translucent polyester film When background illuminators were mounted this arrangement provided an evenly illuminated white urface on which the stimuli appeared as sharply limited bright homogenous urfaces when lit but were completely invisible when not lit The LEDs could be exposed on sixteen intensity levels numbered from 1 (the strongest) to 16 (the faintest) The ratio between two consecutive intensity levels was exactly 1 2 This was achieved in the following way The LED were fed with a high frequency DC pulse train According to the Talbot Plateau law flickering light of a high frequency is perceived as a constant light of an intensity equal to the mean of the flickering light The different intensity levels were obtained by dividing this train so that every other pulse was skipped each time the intensity level was decreased by one step

The background illumination was variable but as a standard value 1 0 cd/m^2 was used Also stimulus expo ure time and interstimulus interval



Fig 4 Perimeter P Blind spot stimulus projector B Background illuminators
F Board with LEDs and emi translucent film

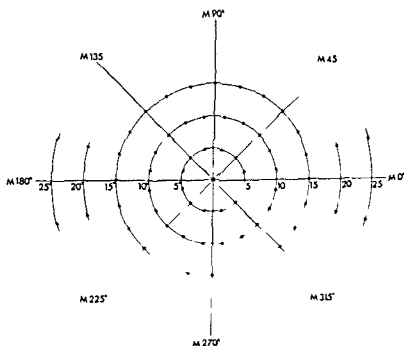


Fig 5 Test point pattern of the perimeter

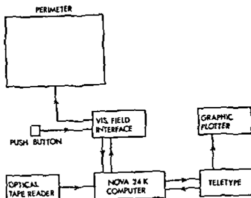


Fig 6 Block diagram of perimeter system

could be changed but throughout this study 0 5 s and 2 0 s respectively w re used In case of an answer from the patient the interstimulu interval was shortened a new stimulus was presented 0 5 s after the arswer The same system for fixation control as in the prototype i e stimuli exposed in the blind spot area was used

The computer system was the same as that described in A but a graphic plotter was added by means of which a visual field chart was drawn in a system of polar coordinates on printed field charts (Figs 6 and 7)

Test logic

a) The threshold wa first estimated at four test points by essentially the same staircase method as that described in A The test process went on until four changes of sign in the test process had been encountered in each of these points

b) As soon as the testing at one test point was completed the threshold measured at this point was transferred to and used as starting level for the test process at a neighbour test point and the threshold was determined after two changes of sign In this way the test proceeded until all 64 points had been tested This arrangement takes advantage

of the a priori knowledge that the thresholds of neighbour points in the visual field are as a rule close to each other

c) The points under testing were shown in random order

Experiment and material

21 eyes with pathological and normal fields were examined by meticulous manual perimetry with the Goldmann instrument kinetic and in some cases static and by automatic perimetry

Results and discussion

1) In seven eyes which had normal visual fields with conventional methods the automatic charts showed smooth almost circular curves

2) In fourteen eyes with definite or suspected visual field defects as examined with conventional perimetry the automatic method either yielded results which were in fairly accurate agreement with those of the manual perimetry (Fig 7) or the defects seemed larger and/or deeper with automatic than with conventional perimetry The stimulus intensity levels of the automatic perimeter are not directly comparable to the stimuli of the Goldmann perimeter but the maximum intensity level of the automatic device (level no 1) at 1 cd/m^2 background illumination can be calculated to correspond to a stimulus between I 4 and II 4 in the Goldmann perimeter In some miotic patients there was such general depression of sensitivity that the maximum intensity level of the automatic perimeter was not seen in large areas In some other cases, however defects appeared on zero level (indicating strongest intensity level not seen) when the automatic machine was used in spite of the fact that Goldmann stimuli corresponding to intensity level 2 or 4 of the computerized perimeter were readily observed by the patient This means that the defects were often more pronounced when plotted with automatic than with manual perimetry an observation later confirmed by Fankhauser (1976)

Two factors (discussed in D and F) may contribute to the explination of this phenomenon 1) a time-dependent increment of contrast thresholds during automatic perimetry which is fairly often seen especially in

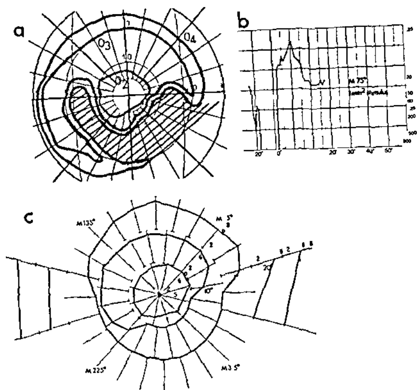


Fig 7 Visual field with glaucomatous defects

a) Central kinetic Goldmann field

b) Static profile

c) Automatic field Results are plotted as polar coordinates and not as isopters Intensity level (i) of the n th test point is represented by a point on the radius from origo through the n th test point Its distance from origo is determined by the intensity level as follows

i units for the first circle (5^0) of 12 points

i+8 units for the second (10^0) circle (20 points)

i+16 units for the third (15^0) circle (24 points)

i 24 units for points at 20^0 eccentricity (4 points)

i 32 units for points at $2{\cdot}^0$ eccentricity (4 points)

Points belonging to the same circle are connected In this diagram intensity level number (0 denoting no response to the strongest intensity level and 8 a low threshold) are marked along the 45^0 and 15^0 meridians (Intensity levels fainter than 8 or 10 are seldom perceived under photopic conditions)

of the a priori knowledge that the thresholds of neighbour points in the visual field are as a rule close to each other

c) The points under testing were shown in random order

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Two factors (discussed in D and F) may contribute to the explanation of this phenomenon 1) a time-dependent increment of contrast thresholds during automatic perimetry which is fairly often seen especially in

d) In four nasal points at 20^{0} and 25^{0} the threshold was determined in the same way as at the four initial points

e) Test stimuli were shown in random order

Manual selective perimetry

The patients were tested with Armaly s selective perimetry in almost the same way as that used by Rock et al (1973) Initially missed paracentral test points were reexposed once The assistant plotting these fields worked under optimized conditions he was fully aware of the fact that all his field charts would be compared with results obtained by other methods he had almost unlimited time at his dispo al etc

Experiment and material

181 eyes in 100 patients from a glaucoma out-patient department were tested with both the automatic and the manual screening method If both screenings were normal the field investigated was considered normal and no further visual field examinations were performed If only one of the two methods showed a pathological result (defined as one or more missed test points) or if both methods showed defects but these defects were not located in approximately the same areas of the visual field the eye in question was rescreened by both methods If on the other hand these defects were located in corresponding area they were confirmed by manual kinetic and static profile perimetry These were also control methods in all doubtful cases

Results and discussion

1) The test time needed for the automatic screening was usually about 4 min per eye with the manual screening it varied from 6 min upward

2) In 47 eyes visual field defects were found All these pathological fields were classified as such by the automatic perimeter One eye was falsely interpreted as normal by manual selective perimetry

3) At first examination the automatic perimeter gave 16 % false positives (i e 16 % of the fields were falsely cla sified as pathological) and the manual method gave 11 % false positives if all initially

pathological fields (compare D) 2) erroneous fixation during manual perimetry, which easily remains undetected, since it may be present only when the stimulus passes into non-seeing areas and which is avoided in automatic perimetry by presenting stimuli in randomized order (compare F)

AUTOMATIC PERIMETRY IN GLAUCOMA VISUAL FIELD SCREENING A CLINICAL STUDY (C)

Examination of the visual fields is necessary in all patients with verified or suspected glaucoma Both diagnosis and treatment depend on whether the patient has normal or pathological fields

A study was undertaken, the aim of which was to compare computerized screening with Armaly s selective perimetry (compare page 15) in order to find out if automatic perimetry could be a practical and time-saving method for detecting field defects in glaucoma

Methods

Automatic perimetry

The automatic perimeter described in B was used

A special screening test logic was designed

a) The threshold was determined by the usual staircase method (compare page 9) at four points at 10^{0} eccentricity Three changes of sign in the test process were required before these thresholds were determined

b) Using these threshold values the computer calculated supraliminal intensity levels to be used for the testing of the remaining test points

c) In each one of the remaining paracentral test points the stimulus was first exposed once on the initial level If it was perceived this time that point was not further tested If it was not seen it was retested according to a certain scheme

TIME CHANGES OF CONTRAST THRESHOLDS DURING AUTOMATIC PERIMETRY (D)

In plotting visual fields i e determining contrast thresholds at a number of points it is often assumed that the probability for perception of a certain stimulus on a certain spot remains stationary during the whole test session in spite of the fact that a decrement of performance has been shown to take place during continuou threshold recording (e g Haider & Dixon 1961 Ronchi & Cetica 1972 Ronchi & Salvi 1973) Such stationarity a least for a limited period of time has also often been assumed in discussions on te t logics for automatic perimetry (Fankhauser et a1 1972 Spahr 1975 Bebie et al 1976 A) Our impression was that this assumption may not be generally valid (A B)

An investigation was performed in order to find out whether important time induced changes of contrast threshold and fixation did occur during automatic perimetry and whether there were differences in this respect between patients and healthy normal test subjects

Methods

The automatic perimeter described in B was used Six out of the 64 test points were used plus the projected blind spot stimulus The contra t threshold was determined by a repetitive up and down staircase method in which the patient answer to a stimulus in a certain position determined the intensity level to be used at next stimulus presentation in the ame point The continuous test which lasted about 30 min was divided into twelve periods In each of the e periods a stimulus was presented ten time at each of the six test points and in the blind spot area The stimuli were exposed in random order within each period

Experiment and material

Twelve healthy normal test subjects and nineteen patients were tested All patients either had a verified diagnosis of glaucoma or glaucoma was suspected In eleven of the eyes tested there were visual field defects

The test situation was the same as in our routine automatic perimetry

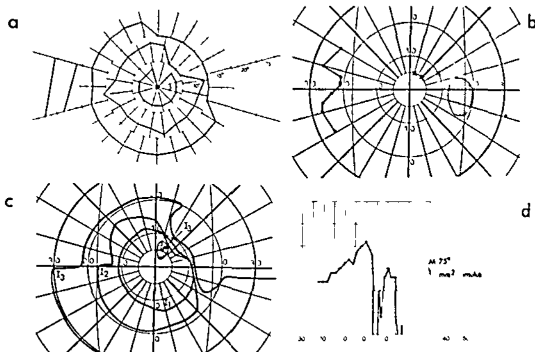


Fig 8 Visual field with glaucomatous field defects a) Automatic screening b) Manual selective screening Crosses indicate points missed at first presentation and at reexposure c) Central kinetic Goldmann field d) Static profile through the 75^{0} - 255^{0} meridian

missed paracentral test points were retested (otherwise 21 5) Re screening reduced the number of false positives considerably to 4 4 and 3 3 % with the automatic and the manual method respectively

4) Out of the 47 pathological visual fields found in this study 20 had been classified as normal on previous controls although most of them had been examined with both the Armaly technique and kinetic perimetry

Thus the automatic glaucoma visual field screening yielded results very similar to those obtained with manual selective perimetry performed under optimized conditions The automatic screening was clearly superior to the routine perimetry as performed at the Eye Clinic in Lund There is reason to believe that these routine examinations are at least of average standard at this clinic

5) In eyes with pathological visual fields the short term variation of the threshold increased with increasing test time

6) In the patient group a moderate impairment of fixation with increasing test time was found

Thus the assumption of stationarity of contrast thresholds during an uninterrupted automatic perimetric test session must be largely rejected particularly in the most interesting cases those with field defects The time dependent threshold changes described may be related to the fatigue-like effect reported by Enoch and co-workers (Enoch et al 1970 Sunga & Enoch 1970)

These changes may imply a disadvantage if very time consuming test logics are used in order to obtain a high reproducibility of measured thresholds There may be cases in which better reproducibility is obtained by a fairly crude test lasting 4 10 min than by a refined time consuming test

However the time changes may also be an advantage By continually exposing stimuli automatic perimetry can be made to put a strain on the patient pos ibly functioning as a provocative test The threshold increments demonstrated during a long test might reflect a functional loss in early developing field defects This theory is supported by the spatial correlation found between test points showing large decrements of sensitivity and documented visual field defects These time-dependent threshold changes may partially explain the discrepancies described in B between defects recorded by conventional and by automatic perimetry

COMPUTER TEST LOGICS FOR AUTOMATIC PERIMETRY (E)

The perimeter de cribed in B had been proved useful for screening but the reproducibility of thresholds measured by this perimeter had not been investigated

As a general rule improved precision at threshold determination is

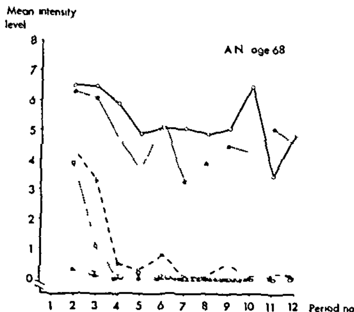


Fig 9 Time changes of the thresholds in a patient with glaucomatous visual field defects The mean of the intensity levels visited during each test period except the first has been plotted for each test point Two test points are located in a scotoma Two test points show large threshold increments with time

Results and discussion

1) A decrement of contrast sensitivity was found to occur with increasing test time

2) *In most subjects this decrement was small, half an intensity level* step (≈1 5 dB) or less during the whole test session It was greater in the patient group than in the normal subjects Many test points in the patient group showed threshold increments of several intensity steps (6 - 10 dB) during the test session (Fig 9) Such a pronounced deterioration of sensitivity was most common in eyes with visual field defects

3) Test points which showed pronounced time dependent threshold increments were often situated in the vicinity of documented visual field defects

4) The threshold deterioration usually remained moderate during the first 4 - 10 min of the test session

1) The starting level of the test process at each point except the first four points was the measured threshold of the preceding neighbour point (as described in Test logic in 8) The te t points were tested until the first change of sign had taken place When this had occurred at a point the last perceived level (i_n) at that point (n) was compared to the measured threshold (i_m) of the preceding point (m) from which the starting level was derived If this difference was less than two ($|i_n - i_m| < 2$) i_n was accepted as threshold Otherwise the testing at point n was continued until two more changes of sign had taken place As soon as the threshold was determined as the last perceived level it was transferred to and used as the starting level for the test process at a new test point When all 64 points were ready-tested the first part of the test was completed and the corresponding thresholds (Thresholds I) were stored in the computer

2) The te t proceeded immediately into the second part of the ession in which thresholds II and III were determined First the test process continued until three changes of sign counted from the start of the session had taken place at each test point (compare Fig 10) Then it was further continued so that four intensity levels after the third change of sign were known for each test point The mean of these four level was calculated by the computer and used as thresholds II Thre holds III were obtained by using the level (i) of the last exposed sti mulus of the test process at each test point or if tha timulu had not been perceived the next stronger level (i 1) (Fig 10) Thus the essential difference between test logics I and III is the number of changes of sign and the number of stimulus exposures in the test pro- cess before the determination of threshold In test logic II a narro wing of the distribution of the measured thresholds is aimed at and an averaging technique is used to determine the threshold

3) During the whole test all stimuli under testing were shown in ran dom order

Experiment

Computer simulations

The three test logics were first tested in computer simulated tests

gained at the expense of increased test time This had been shown to be true for the prototype perimeter (A) However, with that perimeter the test time required even for the longest test logic investigated was only about 5 min , since only fourteen test points were tested The time-dependent threshold increment documented in D made it particularly desirable to investigate the ability of a few different test logics Interest was focused on reproducibility and ability to detect visual field defects

Methods

The automatic perimeter described in B was used

Three different perimetric test logics were compared - one fairly short (Test logic I) and two longer (Test logics II and III) They were *all executed in one test session the short test logic constituted* the first part of the test session The full session was needed for test logics II and III (compare page 30) The same fundamental staircase method as that earlier described was used

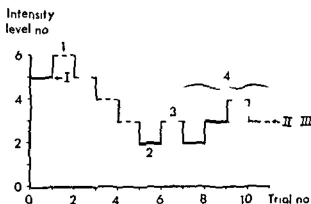


Fig 10 Example of test process at one single point Stimulus intensity level number increa es (i e stimulus intensities decreases) with every answer from the patient (thick horizontal lines) and i crease when no answer is given (broken horizontal lines) 1 2 and 3 denote the fir t second and third change of sign re pectively 4 denotes the four intensity levels the mean of which forms threshold II The last stimulus of the curve (dotted broken line) is not exposed since the patient s answer to this stimulus does not influence the calculation of threshold II I II and III denote thresholds I II and III

1) The starting level of the test process at each point except the first four points was the measured threshold of the preceding neighbour point (as described in Test logic in B) The test points were tested until the first change of sign had taken place When this had occurred at a point the la t perceived level (i_n) at that point (n) was compared to the measured threshold (i_m) of the preceding point (m) from which the starting level was derived If this difference was less than two ($/i_n - i_m/ < 2$) i_n was accepted as threshold Otherwise the testing at point n was continued until two more changes of sign had taken place As soon as the threshold was determined as the last perceived level it was transferred to and used as the starting level for the ʼest pr cess at a new test point When all 64 point were ready-tested the first part of the test was completed and the corre ponding thresholds (Thresholds I) were stored in the computer

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3) During the whole test all stimuli under testing were shown in random order

Experiment

Computer simulations

The three test logics were first tested in computer simulated tests

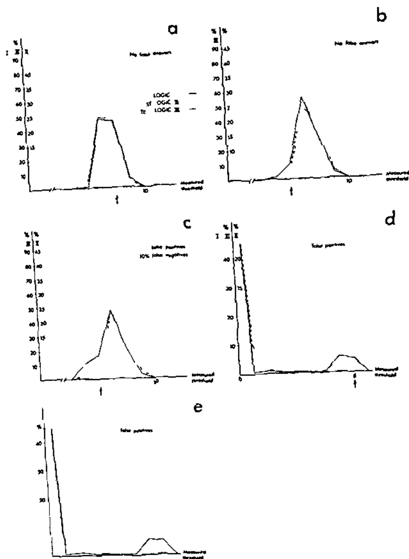
Between the different intensity levels of the perimeter different transition probabilities exist, one set of such probabilities for each test point The transition probability ($p_{i,i+1}$) between intensity level i and the next fainter level i+1 equals the probability-of-seeing of level i The transition probability towards the next stronger level equals $1 - p_{i,i+1}$ False negative or false positive answers from the patient change these probabilities in a way which can be calculated if the mean frequencies of false answers are known

If the test process is repeated using the same probabilities it will end on different intensity levels, thus yielding different values for the measured threshold The distribution of these values depend on the transition probabilities and the test process applied A narrow distribution, a good reproducibility, is aimed at It is of much less interest if the peak of the distribution corresponds exactly to a probability-of-seeing of 0 5, or if it is systematically displaced a short distance from this 50 % threshold

Reasonable transition probabilities for one test point were fed into the computer together with different mean frequencies of false answers This formed the statistical patient models on which the test logics were tried out in computer simulated tests The computer performed 1000 threshold determinations starting from a predetermined intensity level and using the statistical model instead of a patient Thus frequency distributions of the measured thresholds were obtained for the different test logics

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Fig 11 Frequency distributions of thresholds obtained through computer simulated tests The arrow shows the starting point of the test process
a) Test process starts at the 50% threshold No false answers The distributions of thresholds I and III differ very little Thresholds II show the narrowest distribution
b) The process starts a few steps away from the true threshold No false answers All distributions are somewhat displaced in the direction of the starting point Thresholds I are most affected
c) Same starting point as in b False answers occur The distributions are broader than in b Test logic I is most affected



d) Test process starts many steps away from the true threshold which is 0 as in a scotoma False answers occur The results of test logic I are more often erroneous than the results of logics II and III

e) Same test situation as in d The full drawn line shows the distribution of thresholds I (the same distribution is shown in d) The broken line shows the distribution of thresholds I obtained at the second point inside the scotoma when the starting point of the test process is the threshold measured at the first point (full drawn line) The risk of ending at a too low threshold decreases very much at the second point

Between the different intensity levels of the perimeter different transition probabilities exist one set of such probabilities for each test point The transition probability ($p_{i,i+1}$) between intensity level i and the next fainter level i+1 equals the probability-of-seeing of level i The transition probability towards the next stronger level equals $1 - p_{i,i+1}$ False negative or false positive answers from the patient change these probabilities in a way which can be calculated if the mean frequencies of false answers are known

If the test process is repeated using the same probabilities it will end on different intensity levels, thus yielding different values for the measured threshold The distribution of these values depend on the transition probabilities and the test process applied A narrow distribution a good reproducibility, is aimed at It is of much less interest if the peak of the distribution corresponds exactly to a probability-of-seeing of 0 5, or if it is systematically displaced a short distance from this 50 % threshold

Reasonable transition probabilities for one test point were fed into the computer together with different mean frequencies of false answers This formed the statistical patient models on which the test logics were tried out in computer simulated tests The computer performed 1000 threshold determinations, starting from a predetermined intensity level and using the statistical model instead of a patient Thus frequency distributions of the measured thresholds were obtained for the different test logics

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Fig 11 Frequency distributions of thresholds obtained through computer simulated tests The arrow shows the starting point of the test process
a) Test process starts at the 50% threshold No false answers The distributions of thresholds I and III differ very little Thresholds II show the narrowest distribution
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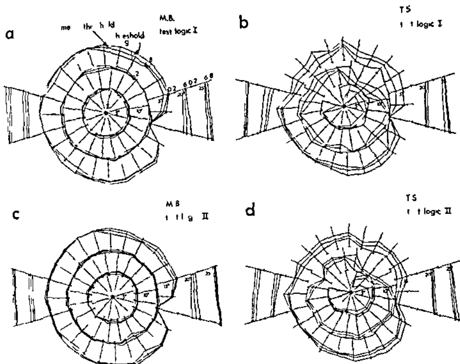


Fig 12 Visual field charts In each chart the mean of the thresholds measured in five test sessions is shown together with the threshold range a) Normal field Test logic I b) Pathological field Test logic I c) Normal field Test logic II d) Pathological field Test logic II

2) The highest reproducibility of measured thresholds was obtained with test logic II and the lowest with test logic I This was in accordance with the results of the computer simulations The variations were of the same magnitude as that found by Bebie et al (1976) and that found in A

3) The standard deviation of the consecutive threshold measurements was considerably smaller in the normal than in the pathological visual fields This difference was so great that the short test logic I generally showed better reproducibility in normal fields than could be achieved by the complicated test logic II in pathological fields (Fig 12)

Measurements on test subjects

Five young normal healthy test subjects and eight patients with verified or suspected glaucoma were tested five times each

Results and discussion

Computer simulations

1) The distributions of thresholds I and III were very similar if no false positive or false negative answers occurred and the starting point of the test process was close to the 50 % threshold (as determined by the transition probabilities) The averaging test logic II showed a narrower distribution (Fig 11 a) If the test process started one or more intensity steps away from the 50 % threshold all distributions tended to be displaced in the direction of the starting point Thresholds I were most affected (Fig 11 b)

2) When there were false answers, the frequency distributions got broader i e the standard deviations of the measured thresholds increased This increment was generally more pronounced in the results of test logic I than in the results of the other test logics (Fig 11 c) A critical test situation arises when the test process starts a couple of steps away from the patient s threshold zone and false answers occur as when a test point in a small scotoma is tested in an unreliable subject Then the starting point of the test process is a normal threshold transferred from a neighbour point outside the scotoma False positive answers from the patient will then sometimes lead to the determination of a falsely low threshold particularly when test logic I is used since with this logic only one change of sign frequently precedes the threshold determination (Fig 11 d) However the risk of obtaining a too low threshold decreases very much at the second point tested inside the scotoma since the starting point of the test process at this second point is the threshold measured at the first test point in the scotoma (Fig 11 e)

Measurements on test subjects

1) The mean duration of the full test session containing all three test logics was 20 38 min The mean duration of the first part of the test in which test logic I is completed was 8 59 min

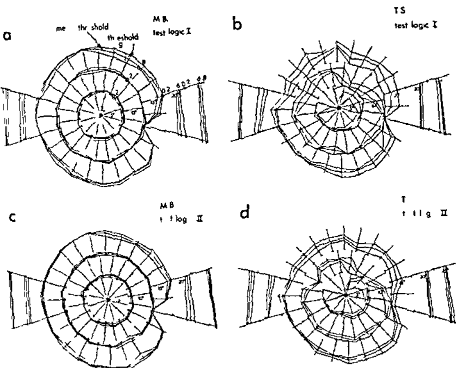


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4) The variation was significantly smaller in the central (5^0) than in the more peripheral (15^0 - 25^0) test points

5) The results of the three logics showed no difference in the ability to detect pathological field defects Though often small, the defects were readily detectable in all charts regardless of the test logic used However the physiological blind spot was more safely detected in the charts of test logics II and III than in the charts of the simple test logic I, just as could be expected from the results of the computer simulations

6) The results of the present study did not show any time-dependent threshold deterioration (as treated in D) to such an extent that the results of the time-consuming, averaging test logic II showed greater variation than those of the short test logic I Such deterioration was however present in the group of eyes with pathological fields, and it was further found that the mean threshold increment per min was close to that found in a similar group of eyes in D

The general conclusion was that it is practical and justified to use a short and fairly simple test logic (like logic I) for the testing of glaucoma suspects, if no visual field defects have earlier been documented in the eye examined However a more advanced test logic, e g using averaging (like test logic II) is favourable for the follow-up of pathological fields when maximal reproducibility is desirable

A NOTE ON FIXATION DURING PERIMETRY (F)

In C it was shown that many visual field defects earlier missed by routine perimetry kinetic or the Armaly technique were detected by automatic perimetry In B it was demonstrated that visual field defects sometimes seemed larger and/or deeper when plotted by automatic than with kinetic perimetry

A difference between the automatic and the manual test which at least partially might explain these discrepancies is the fact that the test object appears at random locations during automatic perimetry but in

a more or less ordered predictable sequence in manual perimetry When the stimulus is presented in a predictable way it might be tempting for the patient to change his fixation slightly when not seeing the stimulus In fact it had been noted that small fast eye movements in the direction of the disappearing stimulus could be seen in the telescope of the Goldmann perimeter when a test object passed a border of a scotoma from a seeing to a non-seeing area

A study was undertaken in order to document the existence of this phenomenon and to find out whether it might be avoided in automatic perimetry by using randomized stimuli

Methods

Kinetic perimetry

By means of EOG eye movements were electrically recorded during kinetic perimetry A slightly supraliminal timulus was moved at constant speed (usually $3^0/s$) centripetally through the visual field The patient was instructed to keep his gaze steady on the fixation target of the perimeter and to signal if the stimulus disappeared At least two meridians were repeatedly tested in each patient one passing only through seeing areas the other crossing either the blind spot or a known glaucomatous scotoma

Automatic perimetry

The automatic perimeter described in B was used

wo different perimetric test logics were compared The first was almost identical to the glaucoma screening logic described in C exposing the stimuli in random locations The second used the same test procedure as the first but the stimuli were hown in sequence instead of being randomized The projected timulus of the blind area was not used in either of these logics

The automatic perimetry was performed in the usual way The patients were instructed to look steadily at the fixation light during the whole test and to pre s the button when perceiving a timulus

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The automatic perimetry was performed in the usual way The patients were instructed to look steadily at the fixation light during the whole test and to press the button when perceiving a stimulus

Material

Eleven patients were examined with the kinetic method, ten with the automatic Seven of the patients were examined with both methods All patients had verified or suspected glaucoma

Results and discussion

1) In seven of the patients examined by kinetic perimetry there was a distinct difference in fixation when the stimulus passed through seeing and non-seeing areas These patients usually maintained good fixation as long as the stimulus moved through seeing areas, but when it passed into a scotoma they often, obviously unconsciously, changed their fixation in the direction of the stimulus and then quickly resumed fixation again (Fig 13) Thus they did not lose" the stimulus and did not signal its disappearance

2) In six of the patients examined with the two automatic test logics it was found that with the second test logic, in which the stimuli were exposed in an ordered predictable sequence, maller defects were recorded than with the first, randomized test logic Sometimes the defects were even unrecognizable in the charts of the second logic In no case were the defects recorded with the first logic smaller than those of the second

The experiments showed that through malfixation scotomata of blind spot size or even larger are easily missed at kinetic perimetry The importance of extremely careful monitoring of the patient s fixation in manual especially kinetic, perimetry is evident It is likely that the same malfixation' comes to the fore also in automatic perimetry, but that such eye movements can largely be prevented by randomization of stimuli

The impression from the first investigation (A) that a test logic with randomized stimuli should be preferred to a non randomized one had thus been supported It is most likely that the randomization of stimuli is one explanation of the superiority of the automatic device to 'routine" perimetry in glaucoma visual field screening (C) It also seems likely that the larger scotomata often found by automatic peri

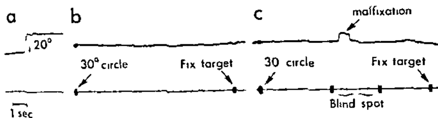


Fig 13 Recordings of eye movements (upper tracings) Markings (lower tracings) a) Calibration 20° horizontal eye movement b) Stimulus moving through seeing areas No eye movements c) Stimulus moving through blind spot Malfixation when stimulus disappears into the blind spot area

metry as compared with kinetic perimetry (B) may at least partially be explained by the observed malfixation during the kinetic examination

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Starting from experience gained from a fairly simple prototype a computerized fully automatic perimeter primarily intended for glaucoma visual field screening and control was constructed The perimeter has 64 static stimuli (light emitting diodes) located in the central visual field

For this perimeter a glaucoma screening test logic was designed and used in a clinical study The results of this computerized screening were very similar to those obtained with a slightly modified version of Armaly s selective perimetry performed under optimal conditions The results of the automatic perimetry were superior to those obtained by routine perimetry a considerable number of previously undetected field defects were revealed by the computerized screening and no known defect was missed by it

With the same perimeter three different test logics for threshold determination were tested on glaucoma patients and healthy normal test subjects Computer simulated tests were also used in order to clarify the theoretical effects of the logics The best reproducibility was obtained with a fairly time consuming test logic in which an averaging technique was used for the threshold determination There was no difference between the different test logics in the ability to detect the pathological field defects investigated All the e defects were revealed by all three logics but the physiological blind spot was more safely detected by the complicated fairly time consuming test logics than by a hort and fairly simple logic Thus such a short logic is sufficient for the testing of glaucoma suspects in whom no field defects have been earlier documented while a more complicated and time consuming test is preferable for the follow up of field defects

The influence of test session duration on recorded threshold and fixation was studied in patients and healthy normal test subjects during approximately 30 min of continuous automatic perimetry A decrement of contrast ensitivity was found to occur with increasing te t time

ADDITIONAL COMMENTS

It must be pointed out that the perimetric system described is but one of many set-ups possible for automatic perimetry Nevertheless the present equipment has turned out to be reliable and simple in operation

The test logics recommended here have certain advantages and have proved useful in practical experiments on patients From an information theoretical point of view Spahr (1975) has analysed some problems of test logic optimization This does not mean that the problem of optimal examination strategy has been solved A generally optimal test logic for clinical use can hardly be constructed since many patient parameters must then be known e g the width of the threshold zone frequency of false answers and time-dependent threshold deterioration Instead it may be preferable to use different test logics in different situations more complicated in such patients who probably have visual field defects and simpler in cases in which the risk of field defects is low (*E*) *We feel that future improvements in test logics have to be* based mainly on practical measurements on patients and not on computer simulated tests

When the size of the steps between the intensity levels of the automatic perimeter (B) was determined practical results from the prototype perimeter (A) were available The step size should be small enough to allow the recording of all clinically significant deviations from the normal but not so small that test time is wasted with only a seeming gain of precision Smaller steps than those used would be of no avail in the screening logic described in C In the test logics for threshold determination (E) the advantage in using smaller steps would be insignificant and would not motivate the number of extra trials needed since the width of the threshold zone in most patients comprises two or more intensity steps of the size used

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I am further indebted to

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Mr Per Westergren instrument mechanic who was responsible for all mechanical details needed in the construction of the perimeters

Miss Louise Goldberg for drawing the figures and for operating the automatic perimeter during many test sessions

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This decrement was small in most subjects, but in many test points mainly in pathological fields a pronounced decrement of sensitivity occurred during the test session Such points were often situated in the vicinity of documented visual field defects A moderate deterioration of fixation with increasing test time was found in the patient group

A 'scotoma-induced malfixation" was documented during conventional kinetic perimetry Fast, small eye movements in the direction of the disappearing stimulus often occur when a slightly supraliminal stimulus is moved into a non-seeing part of the visual field Because of this malfixation' scotomata of blind spot size or even larger are easily missed by kinetic perimetry Experiments with automatic perimetry showed that visual field defects often appear smaller in field charts obtained when stimuli are exposed in an ordered predictable sequence, than when a test logic in which the stimuli are shown in random order is applied Scotomata may even be completely missed when a non-randomized logic is used It is likely that this is due to the same type of malfixation as that demonstrated during kinetic perimetry and that such eye movements are largely prevented by the preferred randomization of stimuli

The computerized perimeter constructed thus proved to be useful for glaucoma visual field screening and for threshold determinations Such a device may quite well take over a considerable part of the perimetric work

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The Clinical Classification of Maculopathies in Adults

A SURVEY

by

Thomas Rosenberg, Svend Faurschou
and Norman Nielsen

SCRIPTOR COPENHAGEN 1977

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The development of fluorescein angiography and the introduction of laser technology into the treatment of macular diseases has considerably widened our knowledge of the pathological processes in the macular re gion A number of clinicopathological reports have confirmed the angio graphic findings and interpretations
The aetiological factors that lay behind the clinical lesions are however still unknown
The clinical pictures have, as a result of the above more relation to the histological than to the aetiological classifications
Clinical classification includes an analysis and categorization of the indi vidual diseases This process takes place daily in the surgery of every ophthalmologist by means of the ophthalmoscope
The ophthalmoscopical examination is enhanced by knowledge of the angiographic picture of the lesion. This means that in the great majority of cases it is possible using the ophthalmoscope alone to evaluate the type and anatomical localization of the pathological lesions Fluorescein angiography is the most important single supplementary examination, both with regard to the diagnosis, indication for treatment and the follow up
The present work describes 9 clinically and histopathologically well defined lesions, which isolated or in combination are seen in the majority of adult macular diseases

Key words review – macula – classification

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Introduction

The classification of diseases is a theoretical system based on certain fundamentals of which the most important are: Morphology, function, age and heredity. Previous classifications of maculopathies have, in the main, been descriptive categorization of clinical entities. Increased knowledge of histopathological lesions and patho-physiological disturbances in function within the last ten years have provided the opportunity of a wider understanding of macular diseases. Gass (1970) and Maumenee & Emery (1972) have been pioneers within this field. A common feature of both earlier and newer classifications has been an almost complete lack of knowledge as to the aetiological factors.

A number of studies having a clinical, experimental and speculative basis have treated the apparent predilection of retinal pathological processes to the macular region ("Locus minoris resistentia", "The exaggerated macular response" (Wise & Wangvivat 1966), "Watershed theory" (Hayreh 1975)). The stereotype reaction to different aetiological factors has also often been stressed (Wessing 1975).

The clinical classification is a diagnostic process involving a specification of the individual disease entity.

The degree of diagnostic effort depends on the object of the diagnostic process. Clinical classification in ophthalmic practice results in a number of procedures in each individual case. Information regarding the patient supplementary examination and treatment.

The introduction of fluorescein angiography has radically changed the [illegible] and understanding of the pathological process in the macular region, further the possibility of laser treatment has changed the object of the diagnostic process.

New reasoning with regard to clinical classification must, in order to pro[illegible] the patient, be disseminated and incorporated in ophthalmic practice without unnecessary delay. This task is a difficult one.

The following survey of some important types of macular lesion in adults is based on ophthalmoscopic [illegible] and evaluation of the pathological processes [illegible] advancement achieved within later years [illegible]

diminish with age and are absent in a large part of the adult population The perivascular reflexes that result from the surface structure and nerve fiber reflexes also diminish with age

Abnormal reflexes occur as stationary reflexes (Vodovozov 1976) in contrast to the physiological reflexes that follow the movements of the light source These are dot like glinting *Munzenformige* reflexes of 20 to 50 μ in size linear reflexes Sternfalten or a more diffuse reflex increase shining as a varnished fundus or glittering as crinkled cellophane In the more advanced cases greyish veil like preretinal membranous sheet occur

Abnormal reflexes are described by a number of terms that are in part influenced by ideas as to how the reflexes occur Cellophane retinopathy macular pucker Sternfalten Retinitis epiretinal fibroplasia

Histopathological studies of two idiopathic cases (B llhorn et al 1975) have demonstrated in agreement with the studies of premacular fibrosis (Roth & Foos 1971 Gass 1976) that abnormal reflexes result from a cellular preretinal membrane The cells are neuroglia with histochemical and ultrastructural features similar to fibrous astrocytes Neuroglia grow through breaks in the internal limiting membrane Spontaneous retractions in the preretinal glial membrane are the cause of folds of the inner retinal layer thus causing linear like reflexes

Clinically preretinal macular fibrosis (Wise 1972) das zentrale vitreoretinale fibroplastische Syndrom (Vodovozov 1976) Surface wrinkling retinopathy (Roth & Foos 1971) occur as a uniform reaction to many different stimuli

Surface retinopathy is more frequently described as a complication to retinal and lens surgery (Tannenbaum et al 1970) posterior vitreous detachment (Jaffe 1967) vascular disease (Gass 1968a) and apparently also occur idiopathically (Speiser 1975) The condition is common in old age but is not uncommon in the initial stages during the 4th and 5th decennium

The importance of surface retinopathy apart from its frequent occurrence is its detremental effect on the central vision together with complications such as cystoid retinopathy and the formation of macular holes Angiographic examination will often be indicated owing to these complications and in order to demonstrate any retinal vascular lesions In slight cases of surface retinopathy fluorescein angiography will be normal

Case SAS 140606 surface retinopathy

0 year old woman with slight hypertension and myxoedema Reduction in vision of the left eye for 4 to ? years

March 1966 oculomotor palsy which disappeared spontaneously

Visual acuity of right eye 6 6 +1 5 sph The macula of the left eye was the site of extensive reflexes slightly greyish and with indistinct contours The practicing

Introduction

The classification of diseases is a theoretical system based on certain fundamentals of which the most important are Morphology function age and heredity Previous classifications of maculopathies have in the main been descriptive categorization of clinical entities Increased knowledge of histopathological lesions and patho physiological disturbances in function within the last ten years have provided the opportunity of a wider understanding of macular diseases Gass (1970) and Maumenee & Emery (1972) have been pioneers within this field A common feature of both earlier and newer classifications has been an almost complete lack of knowledge as to the aetiological factors

A number of studies having a clinical experimental and speculative basis have treated the apparent predilection of retinal pathological processes to the macular region ("Locus minoris resistentia The exaggerated macular response (Wise & Wangvivat 1966) "Watershed theory" (Hayreh 1975)) The stereotype reaction to different aetiological factors has also often been stressed (Wessing 1975)

The clinical classification is a diagnostic process involving a specification of the individual disease entity

The degree of diagnostic effort depends on the object of the diagnostic process Clinical classification in ophthalmic practice results in a number of procedures in each individual case Information regarding the patient supplementary examination and treatment

The introduction of fluorescein angiography has radically changed the attitude to and understanding of the pathological process in the macular region further the possibility of laser treatment has changed the object of the diagnostic process

New reasoning with regard to clinical classification must in order to profit the patient be disseminated and incorporated in ophthalmic practice without unnecessary delay This task is a didactic one

The following survey of some important types of macular lesion in adults is based on ophthalmoscopic recognition and evaluation of the pathological processes in the macula in the light of advancement achieved within later years in this field

1 Surface Retinopathy

The majority of reflexes from the retina originate from the transition zone between the retina and vitreous body i e from the limiting membrane which normally has an intimate relationship to the surface of the retina

The normal" reflexes foveolar reflexes and the foveal ring reflex


C1


C2


C3

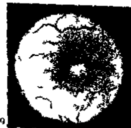

C4


C5


C6


C7


C8


C9


C10

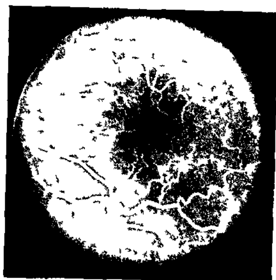


Fig 1

SAS 140606 surface retinopathy left eye Angiography 12th October 1976 *82 sec* Note the taut vessels from the disc in towards the macula and the tortuous parafoveal vessels both arterioles and venules There is no exudation nor *hypertensive* arteriolopathy The poor technical quality results from blurring of the preretinal gliosis

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Fig C 1 SAS 140606 Surface retinopathy left eye October 1976

Fig C 2 LLS 130409 Haemorrhagic choroiditis left eye 31st May 1973

Fig C 3 ELS 130409 Haemorrhagic choroiditis right eye 27th August 1973

Fig C 4 LLS 130409 Haemorrhagic choroiditis left eye 27th August 1973

Fig C 5 ELS 130409 Haemorrhagic choroiditis peripheral scars

Fig C 6 NKM 150824 Foveomacular dystrophy of Gass right eye April 1973

Fig C 7 NKM 150824 Foveomacular dystrophy of Gass right eye November 197[illegible]

Fig C 8 NKM 150824 Foveomacular dystrophy of Gass left eye January 1974

Fig C 9 NKM 150824 Foveomacular dystrophy of Gass left eye November 197[illegible]

Fig C 10 I D 0 0828 High myopia subretinal pigment epithelial neovascularization left eye December 1976

The differential diagnosis must be made with regard to *other conditions* which appear as a clear swelling of the foveal region e g disciform detachment of either the sensory epithelium or retinal pigment epithelium or both and hereditary retinoschisis

Fluorescein angiography should always be carried out if cystoid retinopathy is suspected attention should be paid to late exposures approximately one hour after the injection of fluorescein

3 Macular Holes

Hole formation in the foveal region presents as a well defined lesion Nevertheless this lesion has just as variegated an aetiology as other degenerative retinopathies and numerous patho genetic theories have been suggested (Aaberg 1970)

A hole in the macula is most easily detected ophthalmoscopically by repeated movements of the light over the surface of the fovea In this manner it is possible to observe a discontinuity in the surface by the fact that the normal retinal reflection is absent The diagnosis is made easier by the presence of a) an operculum b) a greyish opaque edge and c) an abnormal reflex or *a spotty pigment epithelial pattern at the bottom of the hole Macular holes* are often circular or ovoid and 100 to 500 μ in diameter

Gass (1976) carried out a histopathological study of an eye with a lamellar macular hole and could correlate the findings to premortal ophthalmoscopic and angiographic observations

Macular holes have been described clinically by Aaberg et al (1970) These are in general seen in the 6th decennium or later The onset of the lesion is often accompanied by a loss of vision or metamorphopsy without any prior observation of a pathological condition In other cases vitreous traction or cystoid retinopathy is present or a history of trauma

The differential diagnosis *is between solitary congenital cysts or large* central cysts in a cystoid retinopathy Spontaneous contractions of the epiretinal membranes during surface retinopathy can simulate macular holes

Fluorescein angiography is a useful tool in the differential diagnosis and it also gives information as to whether the lesion is a full thickness hole or a lamellar hole

4 Retinal Pigment Epithelial Atrophy

The retinal pigment epithelium (RI E) plays a central role in normal retinal function and the appearance of the *RI E* will often reflect the results of a pathological process as the site of a battle will after a war

ophthalmologist referred the patient to our clinic for angiography owing to suspected oedema of the macular region Ophthalmoscopy showed cork screw contortion of the perifoveal venules cellophane and linear reflexes of the macula which was greyish with slight preretinal blurring (Fig C 1) Three mirror examination revealed no vitreo retinal traction nor collapse of the vitreous The angiography was indistinct owing to preretinal gliosis (Fig 1)

2 Cystoid Retinopathy

The ophthalmoscopic picture of cystoid oedema has been known for the last half century One of the classical descriptions was given by Vogt (1918) Interest in cystoid macular oedema has rapidly increased after it became known that the condition was a complication to cataract extraction (Irvine 1953) and is today the most frequent cause of a reduction in visual acuity after a primarily successful cataract extraction The characteristic angiographic picture was described by Gass & Norton (1966) since then a large number of publications have been presented on cystoid retinopathy (Irvine 1976)

The lesion is unique both ophthalmoscopically and angiographically The honeycomb like structure with paler cystoid vacuoles divided by dark septa are best observed in red free light with repeated movements of the light source and indirect illumination of the fovea Cystoid oedema is difficult to see during routine ophthalmoscopy in particular in patients with aphakia where the magnification of the retina is less than in other patients Cystoid retinopathy should be suspected if a reduction in vision is present without any changes in the foveal pigment epithelium

A number of histopathological reports are available in cases of cystoid retinopathy of different aetiology The characteristic picture is multiple cavities lying in the outer plexiform layer inasmuch as the walls of the cysts are formed by compressed and stretched Muller cells and receptor cell axons

Clinically cystoid retinopathy occurs both idiopathically and as a complication to a number of diseases of traumatic inflammatory metabolic and neoplastic nature A common feature of these is apparently a destruction of the blood retina barrier in the perifoveal capillary net

Thus it is hardly possible that there is a common aetiological cause of cystoid retinopathy An interesting observation has been published by Schatz & Patz (1976) who described cystoid maculopathy in diabetic patients that were long standing heavy smokers A peculiar type of cystoid retinopathy was seen in patients with an excessive intake of the B vitamine nicotinic acid (Gass 1973a) In these cases no abnormal vascular permeability to fluorescein was observed

Cystoid oedema does not interfere with the pellucidity of the retina and differs in this respect ophthalmoscopically from other forms of macular oedema (e g opaque retinal oedema in diabetics)

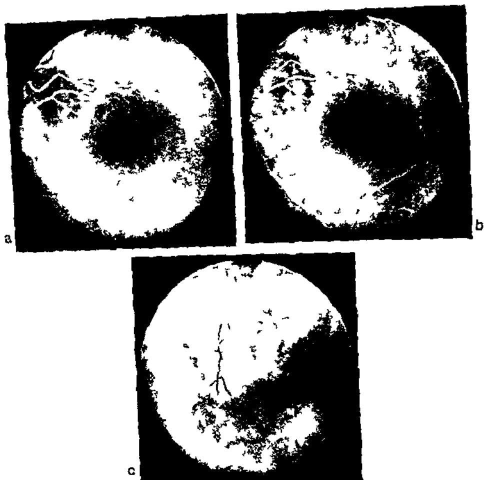


Fig 9
FLS 130403 haemorrhagic choroiditis left eye Angiography 31st May 19/3

a) *18 sec* Disc s zed filling defect close to the *superotemporal* border of the disc A smaller triangular filling defect *one disc diameter* below the foveola Dilatated *capillaries n the disc and subretinal neovascularization in the juxtapapillary focus*

b) *sec* Profuse leakage of fluoresce n from *dilatated capillaries* on the disc and in the ch roiditic focus wh ch s surrounded by *haemorrhage* The fovea is normal S sl ght accumulation of fluorescein can be *seen under the RPE*, corresponding to the fill ng defect below the foveola

c) *sec* Late hyperflu rescence fr m the disc and choroiditic focus.

There is a considerable difference in the appearance of the RPE in various persons and in different parts of the fundus However in the fovea the RPE is so light absorbing within the visible spectrum that details of the choroid are hidden

Clinical classification will often be based on the morphological ophthalmoscopical changes in the RPE The reaction to noxious agents will often be a change in the content and distribution of the melanin granules within and among the cells of the RPE

The basal ophthalmoscopic lesion with atrophy of the RPE is a depigmentation It appears as though the melanin content of the RPE is an indicator of the vitality of the cells The re arrangement of the melanin granules contributes to the polymorphic ophthalmoscopic picture with a conglomerate of depigmentation and hyperpigmentation The terms such as pepper salt reticular butterfly etc have been used to characterize particular types of degeneration The appearance of the degeneration can be of value clinically but rarely gives any information regarding the aetiology

The works of Archer et al (1973) and Hayreh (1975) describe the segmental blood supply of the choroid with watersheds and the mosaic like construction of the choriocapillaris into functional units These observations would appear to explain certain focal lesions of the RPE e g geographic or areolar atrophy

Focal RPE atrophy is a frequent lesion both in the elderly and in young adults The common desire for aetiological diagnosis often results in over interpretation Focal RPE atrophy in younger subjects will as a rule be termed a sequela to choroiditis while a vascular genesis is more probable in the elderly Examples of rather refined diagnoses are toxoplasmosis" in Scandinavia and presumed ocular histoplasmosis in the USA These terms are convenient but do not contain more than a mere descriptive classification of the morphology which in addition is not always well defined

RPE lesions such as those with presumed ocular histoplasmosis including focal haemorrhagic choroidopathy are not not uncommon in Scandinavia unless the histoplasmin skin reaction is negative in these subjects

Diffuse RPE atrophy defined as diffuse loss of pigment in the RPE in the area of the posterior pole can in slight cases be difficult to discover ophthalmoscopically Diffuse RPE lesions can at times be visualized by indirect lighting of the retina in the neighbourhood of the area to be observed In characteristic cases diffuse pigment epithelial atrophy presents as Bull s eye retinopathy (Kearns & Hollenhorst 1966) Once again it is a *question of a* uniform reaction to numerous aetiological factors Bull s eye retinopathy is seen in heredodegenerative diseases toxic lesions and senile atrophy of the RPE Bonnet (1976) The occurrence of diffuse RPE atrophy suggests that the aetiological factor should be sought in the metabolic functions of the RPE













Fig 3

itself exhaustion or blocking of enzymatic reactions This presumption is however purely speculative

Fluorescein angiography is a sine qua non in the evaluation of RPE atrophy The bleaching of the RPE produces a window and permits fluorescence from the choroidal space to pass through and define the exact contours of the lesion

Case ELS 130409 haemorrhagic choroiditis

Female born 1909 1965 to 1968 hospitalized several times for collagen disease with increased sedimentation rate and polymyalgia Treated with prednisone this was discontinued in 1968 owing to arterial hypertension 210/150 mmHg

No eye symptoms until May 1973 when she developed a mild bilateral panuveitis with cells in the aqueous humour and vitreous body The retina was the site of numerous well defined round atrophies of the pigment epithelium of 1/4 disc diameter some of them had a hyperpigmented edge Several 1/2 to 1/1 disc diameter yellow foci in the posterior pole Visual acuity of right eye 6/6 +1 00 sph left eye 6/9 +1 00 sph I o tension 8 and 9 mmHg respectively

Sudden loss of sight to 3/36 and 1/60 in August 1973 Moderate blurring of the vitreous body The macula was the site of haemorrhagic choroiditic foci (Figs C 3-C 4) Treated with prednisone and antihypertensives Despite this the vision deteriorated until February 1974 Vision o u hand movements January 1976 still under steroid treatment Visual acuity of right eye 2/36 left eye hand movements Synechia of the pupil in the left eye Moderate cataract and moderate blurring of the vitreous Widespread diffuse atrophy of the RPE with chorio retinal scars in both maculae together with numerous pigment epithelial defects in the mid periphery The general physical examination produced no evidence to suggest an aetiology of the condition The histoplasmin intracutaneous test in April 1975 was negative

Discussion

A 64 year old woman with a clinical picture of bilateral fulminant haemorrhagic choroiditis complicated by panuveitis The ophthalmoscopical picture of peripheral round atrophies and juxtapapillary and foveal haemorrhagic choroiditis (Figs C 2-C 5)

Fig 3

LLS 130409 haemorrhagic choroiditis right eye Angiography 16th June 1973 (a)-b)) Angiography 27th August 1973 (c)-f))

a) + b) *3) and 96) sec* Discrete pigment epithelial defects in the macula

c) *19 sec* A neovascular area surrounded by haemorrhage beneath the central sub retinal pigment epithelium

d) *24 sec* Filling of the choriocapillaris

e) *54 sec* Diffuse leakage from neovascularization

f) *660 sec* A repeat injection of fluorescein 10 min after the first injection shows absence of filling of the vessel like structures which run beneath the affection in the choroid

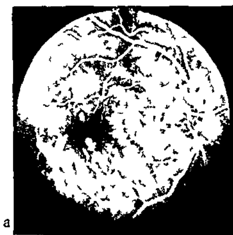












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Fig 3

ELS 130409 haemorrhagic choroiditis right eye Angiography 16th June 1973 (a)–b)) Angiography 27th August 1973 (c)–f))

a) + b) *33 and 963 sec* Discrete pigment epithelial defects in the macula

c) *19 sec* A neovascular area surrounded by haemorrhage beneath the central sub retinal pigment epithelium

d) *24 sec* Filling of the chorio capillaris

e) *34 sec* Diffuse leakage from neovascularization

f) *663 sec* A repeat injection of fluorescein 10 min after the first injection shows absence of filling of the vessel like structures which run beneath the affection in the choroid

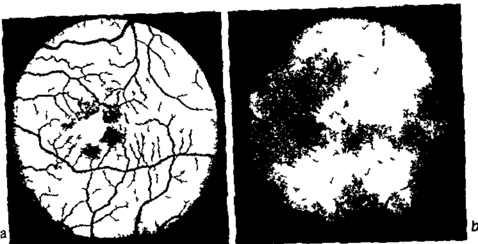


Fig 1

NKM 150824 foveomacular dystrophy of Gass 14th January 1975 left eye

a) Green filter exposure which demonstrate the normal retinal vessels the well defined appearance of the lesion and the surrounding slight atrophy of the RPE.

b) Red filter exposure of the same lesion Better visualization of the pigment accumulation in the exudate like process

6 Foveomacular Dystrophy of Gass

In 1974 Gass (1974) published a clinico pathological study on a peculiar foveomacular dystrophy

The disease is characterized by bilateral round oval or irregular slightly elevated yellow subretinal exudative like lesions often with a small central hyperpigmentation

The lesion as described is not particularly rare The disease often attacks the 30 to 50 year olds its onset is asymptomatic or with metamorphopsy and leads to moderate bilateral loss of vision

The clinical diagnosis has been upto the present and as a rule presenile macular degeneration but the lesion can also simulate vitelliform degeneration of Best

Histopathologically it is a degeneration of the central pigment epithelium together with a deposition of eosinophilic material between Bruch s membrane and the RPE

Angiographically the lesion is characterized by early hyperfluorescence

appears to resemble changes described as »presumed ocular histoplasmosis The ocular changes have a certain likeness to the changes occurring with Vogt Koyanagi disease, but the other symptoms were not present neither was the age characteristic Even though the picture strongly resembles that of an inflammatory disease it is not possible to exclude a vaso occlusive condition of the choroid The vessel like fluorescein empty structures (Fig 8) and the neovascularization would suggest an occlusion of one or more vortex veins as the cause of this clinical picture of haemorrhagic choroiditis

5 Drusen

Drusen is both a histological as well as an ophthalmological diagnosis and as such has been known since the introduction of the ophthalmoscope

Ophthalmoscopically drusen appears as well defined round yellow spots in the RPE varying from 25 to 500 μ

They must be distinguished from punctate hard exudates and punctate pigment epithelial lesions Ophthalmoscopic and angiographic lesions typical of multiple confluent drusen could not in a report by Frank et al (1973) be verified histopathologically This would suggest that the clinical term "drusen is not well defined

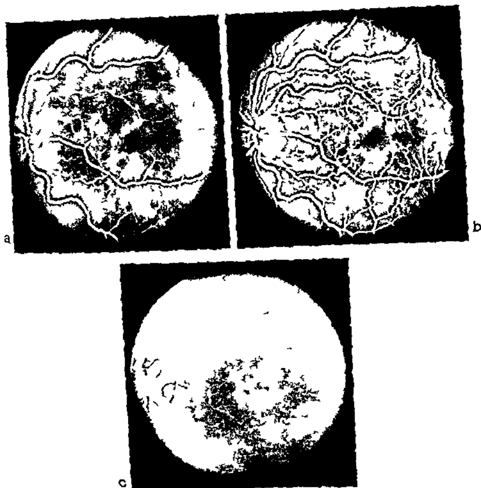
Drusen is considered a normal age phenomenon (senile drusen) and has been described as hereditary inter alia in Hutchinson Tay central guttate choroiditis Doyne s honeycomb choroiditis Holthouse Batten superficial choroido retinitis and malattia leventinese

Gass (1973) considers that it is a question of one and the same heredo degenerative disease Krill & Klien (1965) widened the term by introducing the name flecked retina syndrome" which also includes fundus albipunctatus and fundus flavimaculatus

Histopathological studies have demonstrated that drusen is comprised of an accumulation of hyaline material between the RPE and Bruch s membrane There are a number of theories which place the primary lesion either in the RPE Bruch s membrane or the choriocapillaris Farkas et al (1971) consider drusen formation as a pathologic autolysis of the RPE with extrusion of material from the degenerating pigment epithelial cells into Bruch s membrane

Drusen has clinically been considered a relatively harmless degeneration inasmuch as even a large number of drusen are compatible with retention of the central vision However newer studies all point to a relationship between drusen and disciform macular degeneration (Gass 1973) Normally drusen is progressive over a number of years but can also disappear spontaneously

Photography of the fundus and fluorescein angiography are particularly well suited forms of examination with a view to quantitative evaluation and an opinion as to eventual transition to a more extensive degeneration



Fig

NKM 1508 4 Foveomacular dystrophy of Gass left eye Fluorescein angiography 14th January 19 5

a) *1 sec* Early fluore ence of RPE atrophy in the *periphery of the* process

b) *15 sec* In the arteriovenous phase the lesion can be seen as a contrasting non fluorescent area against a background of hyperfluorescence

c) *14 8 sec* Diffuse accumulation in the pro ess dark *areas* corresponding to the central hyperpigmentation

7 Placoid Pigment Epitheliopathy

Placoid pigment epitheliopathy (PIE) is to be found among the newer clinical entities this similar to the above was described by Gass (19o7)

The ophthalmoscopical picture consists of multiple round approximately

corresponding to a thinning of the RPE and late fluorescence as a result of diffusion of the stain through Bruch's membrane into the subepithelial material. There is a possibility that this clinically well defined picture is merely a solitary giant drusen situated beneath the foveola. The early age of the onset, the symmetrical occurrence, the absence of any other drusen in the eye and the rare transition to disciform degeneration of the macula however point on the contrary.

Case NKM 150824 foveomacular dystrophy of Gass

Male 47 years old, onset of eye symptoms in the middle of 1972 with metamorphopsy and positive scotoma of the right eye. February 1973 metamorphopsy also developed in the left eye in addition to hypersensitivity to light and slow restitution after strong light stimulation. Visual acuity of right eye 6/12 +0.25 sph ⊂ -1.00 cyl 90°, of left eye 6/6 +0.25 sph ⊂ 2.00 cyl 90°. Ophthalmoscopy and three mirror examination revealed slightly elevated, sharp edged, well defined 1/3 disc diameter yellowish subretinal »exudate« in the right fovea. A diffuse central hyperpigmentation could be observed in the process. There was a slight discolouration of the surrounding RPE. No drusen were present and the retinal vessels were normal (Fig. C6). On the left side several small almost confluent yellow patches could be observed together with central hyperpigmentation around the foveola (Fig. C8). There were no signs of inflammation. No effect could be obtained from 60 mg of prednisone daily for 10 days. The Ishihara test was normal. His vision gradually decreased to 6/18 in the right eye and 6/9 in the left eye by April 1974, when 48 photocoagulations were carried out at the edges of the process in the right eye using argon laser.

A slight additional reduction occurred in the vision until September 1976, when the lesion in the right eye looked somewhat like a localized defect in the RPE without exudate. On the left side the process looked like the initial lesion in the right eye (Figs. C7 and C9). The general condition of the patient was normal apart from a history for many years of a gastric ulcer.

Discussion

The initial clinical diagnosis was posterior uveitis. This diagnosis is however not very probable inter alia because of the well defined character of the lesion, the bilateral occurrence, the absence of inflammatory cells in the vitreous body and the absence of any effect from the steroid treatment. Best vitelliform degeneration is not very probable because of the age of the patient and the initial lesion on the left side which did not have the appearance of an egg yolk. The process did not have any similarity to disciform serous detachment of the RPE and subretinal pigment epithelial neovascularization was not observed. Presenile degeneration is often accompanied by drusen and peripapillary atrophy of the RPE, both of these were absent in the present case. The clinical picture fits the description published by Gass with regard to 1) the initial asymptomatic lesion followed by metamorphopsy and a slight reduction in vision, 2) the age, 3) the symmetry, 4) the slow progression, 5) normal colour vision. The picture only differs from that described by Gass in that the lesion in this case was straight edged whereas that of Gass was rounded or oval. EOG was not performed.

8 Disciform Serous Detachmen of the RPE

The term disciform degeneration of the macula was introduced in the first quarter of this century (Oeller 1905 Junius & Kuhnt 1926) and has won universal acknowledgment as the term for elevated oval exudative haemorrhagic or fibrous lesions of the posterior pole mainly in the elderly

A number of studies have been published regarding the pathogenesis of the conglomerate of retinal and subretinal lesions among them Verhoeff & Grossmann (1937) The histopathological materials have however only included the late stages of this degeneration in the eye removed post mortem or owing to suspected malignant melanoma

It was first with the introduction of fluorescein angiography that attention was focussed on the detachment of the RPE as an early lesion in the development of disciform degeneration of the macula Detachment of the RPE was undoubtedly included earlier in the more diffuse term macular oedema until the work of Maumenee (1965) and Norton (1965) emphasized this well defined clinical and angiographic picture which has been described in detail by Cass et al (1966) and Maumenee (1967)

Disciform detachment of RPE is characterized ophthalmoscopically by 1/4 disc to several disc diameters in size slight elevations of the retina absence of foveal reflex (if the fovea is affected) possibly slightly mottled pigmentation and a discrete annular reflex in the periphery of the process The serous character of the process can be demonstrated by indirect illumination whereupon it appears as a translucent bleb The disease mo t often affects the fovea or parafovea but can be seen all over the posterior pole at times multiple lesions may be present

Histopathologically an early detachment of the RPI is characterized by eosinophilic material lying between the RI E and Bruch s membrane (Maumenee 1967) In the case described by Frank et al (1973) the fluid beneath the RPF was lying between the intact basement membrane of the RPE and that of the choriocapillaris i e within the substance of Bruch s membrane The pathogenetic factors responsible for this detachment are unknown

Gass (1970) considers a haemodynamic mechanism to be responsible whereas Hogan (1967) places the primary lesion in Bruch s membrane and emphasizes the absence of histopathological lesions in the choroid The choriocapillaris has normally a high permeability and it is not easy to imagine a haemodynamic or hydrostatic force that can bring about a dissection of the RPF from Bruch s membrane

Clinically an early recognition of the isolated serous detachment is important owing to the relatively good prognosis following early treatment (l Esperance 1971 Schatz & Patz 1973) This is in contrast to the considerable risk of cystoid retinopathy subretinal bleeding and organization of the exudate

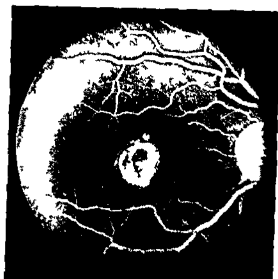


Fig 6
NKM 150824 foveomacular dystrophy of Gass right eye Fluorescein angiography
25th November 1975
382 sec Atrophic stage of the process

1 mm creamy yellowish white lesions located in the pigment epithelium at the posterior pole PPE occurs in young adults with a rapid onset of disturbances in vision and reduction in visual acuity

A similar picture was described by among others van Buskirk et al (1971) Bird & Hamilton (1972) and Fishman et al (1974) who suggested an underlying focal choroidal vasculopathy

The similarity in the size and distribution of the lesions to a functional choriocapillary vascular unit would suggest that PPL is localized infarction of the RPE due to arterial occlusive disorders (Hayreh 1976) The ophthalmoscopical picture can hardly be said to cover any single or aetiological entity thus Bird & Hamilton (1976) distinguish between 4 types of pigment epitheliopathies

Clinically the ophthalmoscopic picture is often attributed to different forms of collagen disease malignant hypertension toxaemia of pregnancy anaesthesia penicillin allergy and sympathetic ophthalmia It appears to have been rendered probable that fibrinoid necrosis of the precapillary arterioles is a common denominator in the pathogenesis of PPL

Angiographically the foci are characterized by initial filling defects in background fluorescence followed by a long standing picture of placoid hyperfluorescent areas corresponding to the ophthalmoscopic lesions They often disappear with complete visual recovery despite patchy depigmentation at the site of the initial processes

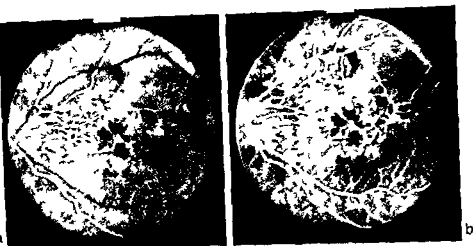


Fig 7

ED 0500328 high myopia, subretinal pigment epithelial neovascularization left eye
Fluorescein angiography 30th December 1976

a) *11 6 sec* Large plaques of newly formed vessels arranged in at least 4 bundles above the fovea which is the site of *haematogenic hyperpigmentation* The *filling* of the choriocapillaris is remarkably intact

b) *15 8 sec* *Diffuse leakage from areas of subret nal neovascularization*

Case ED 050328 subretinal pigment epithelial neovascularization

48 year old female high myopia since childhood In 1961 the visual acuity of the right eye was 6 18 c c left eye 6 6 c c A sudden decrease in vision of the left eye to 6/18 c c occurred in 1965 th s was treated by a practicing ophthalmologist with prednisone The vision then improved to 6/9 c c in the left eye Metamorphopsy of *the same eye suddenly developed in 1974 An add tional reduction in vision took* place in 19 6 V su al acuity of the right eye was 6/30 −14 50 sph ⊂ −1 00 cyl 60° left eye 6/30 −11 5 sph ⊂ −1 00 cyl 110° Ophthalmoscopy showed normally vascularized optic d sc peripapillary atrophy of the RPE and choroid spotted atrophy and hyperpigmentation (Fuch s spot) in the macula (Fig C 10)

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with scar formation which is characteristic of disciform degeneration of the macula It is not uncommon to find an asymptomatic lesion in the fellow eye of an eye with advanced degeneration

Angiographically disciform serous detachment of the RPE is characterized by early and long *standing* hyperfluorescence in the area of detached RPE despite the fact that this is ophthalmoscopically intact The explanation of this hyperfluorescence is a possible change in the permeability of the loosened *pigment epithelium* with fluorescein staining of the cytoplasm (Gass 1970) In pure cases of detachment of the RPE the choroido retinal barrier remains intact

9 Subretinal Pigment Epithelial Neovascularization

Macular haemorrhage almost inevitably results in a visual catastrophy The ophthalmologist will therefore normally be presented with the lesion shortly after the onset

A haematoma below the RPE appears ophthalmoscopically as a slate grey, greenish brown tumour like mass at times it has a striking similarity to malig nant melanoma There is the possibility today of making the diagnosis by visualizing the proliferating vessels causing the haemorrhage below the RPE

The works of Teeters & Bird (1973) and Sarks (1973) give a broad histo pathological description of subretinal pigment epithelial neovascularization which occurs in connection with and most probably as a result of flaws in the membrane of Bruch

Even though the fluorescein angiographic method is not optimal for the visualization of pathological processes lying beneath an intact RPE the method has been of considerable help in visualizing subretinal neovascular membranes (Gass 1973b Schatz & Patz 1973 Small et al 1976)

Clinically subretinal neovascularization and deep macular haemorrhage can be seen as a complication to angioid streaks high myopia and focal haemor rhagic choroiditis however it is most often met with in senile disciform ma cular degeneration

The fluorescein angiographic picture of subretinal pigment epithelial neo vascularization neovascular membranes or tufts is characterized by a lacy vascular pattern of fluorescence in a spoked or sea fan shaped configuration with the greatest amount of fluorescein leakage at the circumference The hyperfluorescence appears early and then progresses to leakage in the sub sequent phase

Angiography is of inestimable importance in the diagnosis of subretinal pigment epithelial neovascularization which is difficult to identify ophthalmo scopically and essential for the preoperative evaluation of laser treatment

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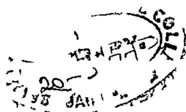
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SUPPLEMENTUM 130

acta ophthalmologica

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Studies on the Mechanism of the Breakdown of the Blood-Aqueous Barrier in the Rabbit Eye

by

Elisabeth Bengtsson

SCRIPTOR COPENHAGEN 1977

Acta Ophthalmologica
SUPPLEMENTUM 130

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University of Lund Lund Sweden

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Oh dear! Oh dear!
I shall be too late!

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1 INTRODUCTION

This investigation concerns the mechanism of the breakdown of the blood-aqueous barrier in the rabbit eye This barrier which maintains the normally low protein content of the aqueous humor has been defined morphologically in the anterior uvea The main objective was to obtain more information about the barrier damaging effect of prostaglandins (PG) and α-melanocyte stimulating hormone (α-MSH) with special regard to the protein leakage across the barrier into the anterior chamber

1 1 Effects of prostaglandin on the blood-aqueous barrier

In acute anterior uveitis in man and in the response of the rabbit eye to irritative stimuli there occurs a set of phenomena miosis va odilatation in the iris and conjunctiva and disruption of the blood aqueous barrier eflected by an increa ed intraocular pre sure and increased aqueous protein These phenomena have been hown to be associated with an increased concentration of prostaglandins in the aqueous humor[1 2] and they can be mimicked by exogenous administration of prostaglandins onto the eye [3 4 5] Ambache[6 7] first demonstrated the presence of prostaglandins in ocular tissues nd it as found by Anggard and Samuelsson that prostaglandins can be formed by the tissues of the iris and ciliary body [8] Biosynthesis of prostaglandins appears to occur upon demand and de novo with a high turnover rate and little cellular storage [9] Many different forms of irritative timuli (for instance paracentesis [10] argon laser irradiation of the iris [10 11] intravitreal bovine serum albumin[1]) to the eye trigger pro taglandin synthesis and release The ocular effects of these prostaglandin mediated stimuli can be prevented by pretreatment with acetyl salicylic acid[10] or indomethacin [12 13 14] known pecifically to inhibit the conversion of prostaglandin E_2 (PGE_2) nd pro taglandin E_1(PGE_1) from the precursors arachidonic acid and dihomo-γ-linolenic acid re pectively [15] Bethel and Eakins[16] have also sho n that the prostaglandin antagonist polyphloretin phosphate i a potent inhibitor of pro taglandin action in the rabbit eye Thus in th r bbit inhibition of barrier disruption by blockade of the pros glandin synthesis or inhibition of prostaglandin



1 INTRODUCTION

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1 1 Effects of prostaglandin on the blood-aqueous barrier

In acute anterior uveitis in man and in the response of the rabbit eye to irritative stimuli there occurs a set of phenomena miosis vasodilatation in the iris and conjunctiva and disruption of the blood aqueous barrier reflected by an increased intraocular pressure and increased aqueous protein. These phenomena have been shown to be associated with an increased concentration of prostaglandins in the aqueous humor[1 2] and they can be mimicked by exogenous administration of prostaglandins onto the eye[3 4 5]. Ambache[6 7] first demonstrated the presence of prostaglandins in ocular tissues and it was found by Anggard and Samuelsson that prostaglandins can be formed by the tissues of the iris and ciliary body[8]. Biosynthesis of prostaglandins appears to occur upon demand and de novo with a high turnover rate and little cellular storage[9]. Many different forms of irritative stimuli (for instance paracentesis[10] argon laser irradiation of the iris[10 11] intravitreal bovine serum albumin[1]) to the eye trigger prostaglandin synthesis and release. The ocular effects of these prostaglandin mediated stimuli can be prevented by pretreatment with acetyl salicylic acid[10] or indomethacin[12 13 14] known specifically to inhibit the conversion of prostaglandin E_2 (PGE_2) and prostaglandin E_1 (PGE_1) from the precursors arachidonic acid and dihomo γ-linolenic acid respectively[15]. Bethel and Eakins[16] have also shown that the prostaglandin antagonist polyphloretin phosphate is a potent inhibitor of prostaglandin actions in the rabbit eye. Thus in the rabbit inhibition of barrier disruption by blockade of the prostaglandin synthesis or inhibition of prostaglandin

action and the enhanced prostaglandin concentration in aqueous humor after barrier damage, and at last induction of the typical uveitis phenomena by administration of topical prostaglandin, all suggest the role of a specific receptor for prostaglandin causing barrier disruption in ocular inflammation

Many of the pharmacologic effects of the prostaglandins become manifest in systems in which cyclic 3'5' adenosine monophosphate (cAMP)is believed to be a mediator of hormonal responses [17, 18] In the adrenal, thyroid, and corpus luteum prostaglandins mimic the effects of the tropic hormones ACTH, thyroid stimulating hormone (TSH) and luteinizing hormone (LH) The effects of the prostaglandins like those of the tropic hormones, are believed to be due to stimulation of adenyl cyclase, the enzyme which generates cAMP Adenyl cyclase [19] and cAMP phophodiesterase,[20] which converts cAMP to the metabolically inactive adenosine 5'-monophosphate,[21] have been demonstrated in ciliary processes and iris tissue The ciliary process adenyl cyclase has been shown to be responsive to PGE_1 and to catecholamines[22] indicating that cAMP is the mediator of the action of these agents

Waitzman & Woods[22] reported that adrenaline (which is a both α- and β- adrenergic agonist) and phenylephrine (primary an α-adrenergic agonist) have a synergistic effect on the PGE_1 induced activation of adenyl cyclase whereas noradrenaline (α-adrenergic agonist) inhibited the stimulation of adenyl cyclase produced by PGF_1 On the other hand Neufeld et al [23] and Radius & Langham [24] found that noradrenaline per se caused an increase of the cAMP concentration in aqueous humor This apparently opposite action of noradrenaline might be explained by the hypothesis that prostaglandins are involved in a negative feedback system modulating the responses to stimulation of the adrenergic nervous system [9, 18] Prostaglandins are released after stimulation of adrenergic nerves and then act to decrease the further release of noradrenaline in response to presynaptic nerv

interaction of the two endogenous systems is reflected by the pupillary diameter response, since degeneration release of noradrenaline after ganglionectomy yields more mydriasis in indomethacin-treated eyes because the negative feed back loop is blocked

It has been proposed that cAMP mediates not only the physiological but also the pathological effects induced by prostaglandins[9,26] The breakdown of the blood-aqueous barrier in rabbits produced by arachidonic acid [27] and prostaglandins[28, 29] can be inhibited by pretreatment of the animals with imidazole which stimulates the enzyme cAMP phosphodiesterase [30] supporting the suggestion that cAMP is the mediator of the action of prostaglandins on the blood-aqueous barrier

The blood-aqueous barrier comprises the entire tissue complex which intervenes between the circulating blood and the aqueous humor in the anterior and posterior chambers of the anterior segment of the eye In the case of the posterior chamber the barrier consists essentially of vascular endothelium and basement membrane, stroma and the two layers of ciliary epithelium Vascular endothelium basement membrane and stroma also make up the barrier in the anterior chamber but whilst the anterior iridial region of the barrier lacks the epithelial component its vessels are non-fenestrated and even lined with r unusually thick basement membrane and the capillaries are surrounded by a vascular sheath or adventitia This is in contrast with the ciliary region where the vessels are fenestrated (for ref see 31)

The location f the disruption of the blood aqueous barrier in uveitis has been a matter of dispute It may occur at the ciliary vasculature or at the ciliary epithelia or both According to Vegge Neufeld & Sears[32] PGE_2 induce changes in the tight junctions that seal the lateral intercellular clefts of the nonpigmented epithelium The e authors did however not settle whether the changes of the tight junctions were due to a direct action of prostaglandins or merely a result of increased hydrostatic pres ure within the ciliary processes On the other hand Federsen and Bonjum[33 34] have reported that the breakdown of the blood-aqueous barrier due to prostaglandins is primarily due to a marked increase of the endothelial permeability of the ves e s in the ciliary processes and iridial e tensions The v scular leakage leads to distension of the epithelial component of he barrier and subsequent disruption of tight junctions between the cells of the inner nonpigmented epithelia lining the poste i r chamber

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intraocular pressure the initial pressure increase was followed by subnormal values [43] High flare values were correlated to high values of the intraocular pressure, the latter preceding the aqueous flare increase indicating that the e two parameters reflect the same mechanism Repeated daily injections of α-MSH were found to cause a successive decrease of the aqueous flare response and at last the animals became completely refractory to α-MSH A rest period of about two weeks restored the previous ability to give a flare response [40]

These authors also compared the barrier damaging effects of α-MSH with those of infrared irradiation of the iris another type of stimuli capable of inducing a barrier breakdown After both types of stimuli they found a strikingly similar histological picture with swelling of the ciliary processes and formation of vesicles in the pigmented layer or between the two ciliary epithelial layers in the processes [44] The electrophoretic pattern of the proteins in the aqueous humor was similar in both instances and similar to the distribution of the serum proteins [45] On the other hand there were also facts indicating that the effects of α-MSH and infrared irradiation are due to different mechanisms Thus neither topical nor retrobulbar anaesthesia inhibited the aqueous flare increase after α-MSH but both diminished the response to infrared irradiation Further rabbits made refractory to the aqueous flare producing effect of irradiation were not refractory to α-MSH [45]

The aim of the experiments described in this summary was

1 to elucidate the role of prostaglandins on the breakdown of the blood-aqueous barrier in the rabbit eye caused by α-MSH as compared to other types of irritative stimuli
2 to define the ultimate mechanism of the barrier disruption produced by different types of traumatic agents

The main part of the inactivation of prostaglandins by dehydrogenation has been assumed to take place in the lungs and liver [35]. The prostaglandin-metabolism in ocular tissues may be negligible and the importance of the absorptive transport mechanism of the anterior uvea described by Bito is thereby emphasized [36]. This prostaglandin-uptake takes place in the ciliary processes [37]. Bito[38] has suggested that the ciliary epithelium has a detoxifying function actively transferring prostaglandins from the interior of the eye out into the blood stream and that a damage of this detoxifying capacity may be an important factor in the pathogenesis of anterior uveitis.

1.2 The barrier damaging effect of α-MSH

It has been shown that α-MSH given subcutaneously contrary to many other traumatic stimuli is capable of producing characteristic uveitis symptoms apparently without any associated increased prostaglandin synthesis since its action cannot be prevented by pretreatment with acetyl salicylic acid[10]. Thus it was claimed that disruption of the blood-aqueous barrier is not always necessarily due to enhanced prostaglandin synthesis and release [10].

Interest in the action of α-MSH on the blood-aqueous barrier started with an observation made by Anjou, Krakau and Stigmar [39]. They found that general administration of a moderate dose of adrenocorticotropic hormone (ACTH) to rabbits caused an increased aqueous flare in the anterior chamber. Later it was shown by Dyster-Aas and Krakau[40] that the flare provoking effect of ACTH was not mediated by the adrenal cortex and that the action was better correlated to the melanocyte stimulating activity than with the corticotropic effect of the peptides tested. α-melanocyte stimulating hormone is composed of 13 amino acids identical with the sequence of the first 13 amino acid of ACTH except for the fact that in α-MSH an acetyl group is coupled with the N-terminal serine and an amino group is coupled with the C-terminal valine. This structural identity explains the melanocyte stimulating activity of ACTH [41]. The flare provoking action of α-MSH has been further analyzed by Dyster-Aas & Krakau. They found a great individual variation in the ability of α-MSH to give an aqueous flare response. Pigmented rabbits were more sensitive than albinos, older animals more sensitive than younger ones and fasting rabbits more sensitive than normally fed animals [40, 42]. α-MSH also influenced the

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2 to define the ultimate mechanism of the barrier disruption produced by different types of traumatic agents

2 MATERIAL AND METHODS

2 1 Animals

All the experiments were performed on adult, pigmented rabbits The animals were kept for at least one week in the rabbit cages at the Eye Clinic before they were used for any experiments They were given a standard diet of pellets and water In the main part of experiments the rabbits were used once, except in a few cases (I) in which the animals were used again for new experiments after at least seven days recovery

2 2 Aqueous flare response (I-VII)

The protein leakage into the anterior chamber caused by different traumatic stimuli to the eye was chosen as principal parameter for quantifying the breakdown of the blood-aqueous barrier The protein concentration in the aqueous humor can be measured by means of a photoelectric instrument The instrument used in this investigation (Technical note in paper I) is a modification of that worked out by Oyster-Aas and Krakau [46] An optical system built like a slit lamp provides a narrow beam of light When this beam passes through the anterior chamber an aqueous flare is produced by scattering by large molecular substances in the aqueous humor The slit lamp is rigidly connected with a system for observing and measuring the aqueous flare An objective lens forms an image of the flare and its surroundings in front of a photomultiplier tube By means of a beam splitter part of the light also reaches the observer The portion of the flare to be measured is so adjusted as to coincide with a mark seen by the observer In front of the photomultiplier tube one fixed and one vibrating aperture are placed The vibrating aperture moves with a frequency of 20 cps, scanning the flare and producing an AC signal from the multiplier tube This signal is fed through a band pass filter (f_0 40 Herz) amplified rectified and recorded on a pen recorder

The dominating part of the flare after a barrier breakdown is caused by proteins and there is a satisfying linear correlation between flare values and normal as well as increased protein concentrations [47] Thus it is possible to obtain a value for the relative

protein concentration in the aqueous humor without destroying the eye by paracentesis a circumstance which makes it possible to follow the aqueous flare response by repeated measurements at suitable intervals during the interesting period of the inflammation The measurements can be performed on rabbits sitting in their natural position and no anaesthesia is needed for any of the experiments The flare values are recorded in arbitrary units and the results are given in absolute units or as a quotient (Q_{max}) between the maximal aqueous flare value recorded after stimulation and the base line flare value A positive aqueous flare response was by Oyster-Aas and Krakau defined as a Q_{max} of $> 1\ 5$ [42] and to make the present results comparable with the studies of those authors the same convention is used in this investigation

2 3 Intraocular pressure (III)

In some series of experiments the intraocular pressure was recorded parallel to the aqueous flare measurements The measurements of the intraocular pressure were performed by means of vibration tonometry [48] The results are given in millimeters of Hg No anaesthesia was needed and the rabbits were sitting in their natural position

2 4 Pupillary diameter (IV VII)

In two of the present studies the changes of the pupillary diameter produced by the irritative stimuli were recorded The measurements were undertaken under conditions of uniform illumination using a clear plastic ruler Vertical and horizontal meridians were mea ured and the average value was noted

2 5 Histological procedures (III)

uitable pieces of tis ue from the anterior segment were o ked in a liquid propane propylene mixture freeze-dried fixed by expo ure to formaldehyde gas embedded in vacuo in paraffin wax sectioned ans stained with hematoxylin and eosin according to standard hi totechnical principles for light microscopy

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3 PESULTS A D DISCUSSION

3 1 The inhibiting effect of indomethacin on the breakdown of the blood aqueous barrier in the rabbit eye (I)

The aim of this part of the study was to follow the course of the protein leakage caused by topical administration of PGE_2 or of its precursor arachidonic acid (AA) and to test the blocking activity of topical indomethacin on the protein leakage caused by these two agents and by infrared irradiation of the iris endotoxin given intravenously and α M H injected subcutaneously

At about 30 minutes after application of PGE_2 or AA distension of conjunctival vessels epiphora and miosis appeared but still no or only a slight increase of the aqueous flare was recorded The flare curve then rose rapidly and reached its maximum after one to one and a half hours after stimulation Pretreatment with topical indomethacin did not affect the aqueous flare response or external irritation caused by topical PGE_2 However indomethacin effectively inhibited the AA-induced protein leakage since the conversion of AA to the barrier damaging agent PGE_2 had been blocked The external irritation caused by AA was also decreased by indomethacin Indomethacin markedly inhibited the barrier breakdown caused by infrared irradiation and endotoxins too and it is suggested that the action of these two stimuli are mediated via enhanced intraocular prostaglandin synthesis (Fig 1)

Neufeld Jampol and Sears[10] found a significant inhibition of the flare response to argon laser radiation by pretreatment of the rabbits with acetyl salicylic acid generally They also reported that the miosis was unaffected by acetyl salicylic acid In the present study topical indomethacin only slightly prevented the immediate miosis which was pronounced already one to two minutes after initiation of irradiation most of which rapidly disappeared within about 10 minutes after the irradiation had been stopped The remaining miosis was sustained in untreated eye for about one hour after which the pupil slowly returned to its initial size during the next hour Pretreatment with indomethacin however almost totally inhibited this sustained miosis i e the pupillary size was restored much more quick indicating that this later component of the pupillary constriction is mediated via prostaglandins As to argon laser radiation[10]

2 6 Uptake of ^{3}H-prostaglandin E_1 (V)

Pieces of the anterior uvea were incubated for 60 minutes in a solution containing ^{3}H-prostaglandin E_1 (1 58 x 10^{-9} g/ml) The tissue pieces were solubilized and counted in a liquid scintillation spectrometer The uptake of ^{3}H PGE$_1$ is expressed as the tissue wet weight/medium ratio

2 7 Aqueous flare provoking stimuli

Disruption of the blood aqueous barrier was elicited by the following stimuli

1 Prostaglandin E_2 (PGE$_2$) (Upjohn Co, USA) topically applied onto the cornea (I, III, IV VI, VII)
2 Prostaglandin E_1 (PGE$_1$) (Upjohn Co USA) topically applied onto the cornea (VI)
3 Arachidonic acid (AA) (Sigma USA) topically applied on the cornea (I, III) AA is precursor of PGE$_2$
4 Infrared irradiation of the iris (I III-V VII)
5 Endotoxin of Proteus mirabilis (Prof H Fritz, Linkoping Sweden) given intravenously(I III)
6 α-MSH (CIBA, Schweiz) given subcutaneously (I-VII)

2 8 The influence of the following substances on the effect of the aqueous flare provoking stimuli was studied

Indomethacin (Dumex, Denmark) inhibits the conversion of prostaglandins from their respective precursors (I)
Imidazole (Sigma, USA) stimulates the enzyme c-AMP phosphodiesterase (II III V)
Noradrenaline (Sigma USA) α-adrenergic agonist (IV
Terbutalinsulfate (Draco Sweden) β-adrenergic agonist IV
Phentolamine (Regitin R CIBA Schweiz) α-adrenergic antagonist IV
Propranolol (ICI Pharma England) β-adrenergic antagonist IV
Tropicamid (Mydriacyl R Alcon USA) anticholinergic agent IV
Polyphloretinphosphate (PPP Leo Sweden) PG-antagonist VI
Diphloretinphosphate (DPP Leo Sweden PG-antagonist VI
Theophylline Theon R Draco Sweden) inhibit the enzyme c-AMP phosphodiesterase (VII)

3 RESULTS AND DISCUSSION

3 1 *The inhibiting effect of indomethacin on the breakdown of the blood aqueous barrier in the rabbit eye* (I)

The aim of this part of the study was to follow the course of the protein leakage caused by topical administration of PGE_2 or of its precursor arachidonic acid (AA) and to test the blocking activity of topical indomethacin on the protein leakage caused by these two agents and by infrared irradiation of the iris endotoxins given intravenously and α MSH injected subcutaneously

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it was not indicated whether the failure of acetyl salicylic acid to inhibit the miosis refers to the immediate pupillary response, the sustained miosis or to both components The discrepance between the studies concerning the miosis may also be due to the fact that the two types of trauma are of different strength Compared with argon laser radiation, after which a burn can be seen on the iris, infrared irradiation is a very faint trauma and not even any histologic changes are seen in the iris at the site of the irradiation [44] When caught on the back of the hand the infrared irradiation is not perceived as painful The immediate miosis can be reduced by pretreatment with local anaesthetics and is probably due to a nervous reflex mechanism [45] Indomethacin given topically may have a slight local anaesthetic effect, which may contribute to the prevention of the reflectory miosis

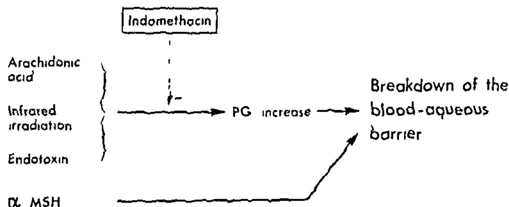


Fig 1 The inhibiting effect of indomethacin on the breakdown of the blood aqueous barrier

The barrier damaging effect of α-MSH could not be blocked by topical indomethacin In fact the highest protein concentrations were seen in indomethacin treated animal This supports the suggestion by Neufeld Jampol and ... [10] that α-MSH contrary to many other stimuli does not exert its effects via increased intraocular prostaglandin-synthesis (Fig 1) Neufeld et al [10] administered acetyl salicylic acid generally (per rectum) thereby excluding the possibility

that the ocular effects of subcutaneous α-MSH might be caused by prostaglandin reaching the eye after synthesis somewhere else in the body Furthermore the main part of prostaglandins in general circulation is inactivated when reaching the lung.[35] It is thus likely that the effects of endogenous prostaglandins in a physiological or even pathological role are locally restricted

3 2 Facilitation by imidazole of the aqueous flare response to α-melanocyte stimulating hormone (II)

Various authors have suggested that cAMP is the mediator of the effects of prostaglandins on the blood-aqueous barrier[9,26] Agents which increase cAMP phosphodiesterase activity are said to antagonize the prostaglandin effects by lowering the cAMP concentration Imidazole stimulates the activity of phosphodiesterase in vitro[30] In agreement with this Zink Podos and Becker[28,29] showed that imidazole administered generally was a potent inhibitor of the prostaglandin-induced intraocular pressure-increase For other biological systems it has been proposed that the α-MSH effects (like the prostaglandin effects) are due to an ability of α-MSH to increase the amount of intracellular cAMP by either stimulating the adenyl cyclase system[49] or by inhibiting the enzyme cAMP phosphodiesterase[50] Thus it could be expected that imidazole would inhibit the ocular effects of α-MSH as well In the present study the effect of topical imidazole on the α-MSH induced protein leakage was tested Surprisingly it was found that topical imidazole had no blocking activity on the α-MSH effects but on the contrary strongly potentiated the flare response to α-MSH It was also found that in rabbits which primarily were non-responders pretreatment with imidazole brought about increased sensibility to α-MSH Furthermore the contralateral eye which had not been pretreated with imidazole got an increased α-MSH responsiveness A similar increase of the α-MSH response was achieved by pretreatment of the animals with topical pilocarpine which contains an imidazole group

Thus the effect of topical imidazole on the α-MSH response was the opposite of the effect of intraperitoneal imidazole on the prostaglandin action reported by Zink Podos and Becker[28] The reason was unclear and at this stage of the investigation it indicated that the barrier damaging effect of α-MSH was mediated in a way different from that of prostaglandin

3.3 *The effect of imidazole on the disruption of the blood-aqueous barrier in the rabbit eye (III)*

In this study the effect of topical as well as of general imidazole on the flare response to α-MSH as compared to other prostaglandin mediated stimuli (PGE_2, AA, infrared irradiation, endotoxins) was tested. It was found that topical imidazole did not interfere with the response to any of the tested stimuli except for α-MSH, whose response was facilitated and potentiated as was reported in paper II. However when administered intraperitoneally imidazole effectively reduced the ocular effects of α-MSH as well as of the other four irritative stimuli. For PGE_2 the intraocular pressure increase was followed parallelly with the flare response. The pressure reached its maximum 30 minutes after stimulation with PGE_2, a point of time when the aqueous flare had just started to rise. The maximum protein concentration was reached at about the time when the intraocular pressure had returned to normal values. Intraperitoneal imidazole almost totally abolished the PG-induced intraocular pressure rise whereas the flare response was reduced with about 50 per cent. Thus pressure rise is not a prerequisite for protein leakage. This is also inconsistent with the assumption that the disruption of the epithelium of the ciliary processes is merely secondary to an increased hydrostatic pressure across the epithelium induced by increased capillary permeability leading to distension of the ciliary processes. These results rather indicate that prostaglandins may have a deleterious effect directly on the epithelium besides its ability to increase the permeability of the vessels reported by Pedersen[34].

The fact that intraperitoneal imidazole inhibits the effect of α-MSH as well as of prostaglandin mediated agents indicates that the different types of stimuli have a factor in common at a stage after prostaglandin synthesis in the chain of reactions. In agreement with the suggestion for prostaglandins[9, 26, 28] the present study indicates that α-MSH may as well exert its barrier damaging effect via increased cAMP activity (Fig. 2).

Still no satisfying explanation to the synergistic action of topical imidazole and α-MSH could be given. A histological examination of the iris and ciliary body of rabbits treated with α-MSH and topical imidazole was of no help in finding the mechanism of this synergism.

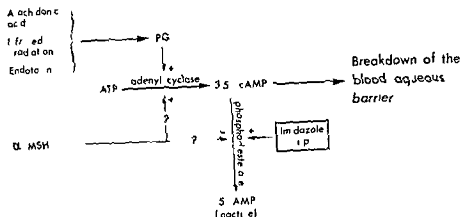


Fig 2 The effect of i traperitoneal im dazole o the breakdown of the blood aqueous ba r er
(p traper to eal)

Intera tion of adrenergic agents with α-melanocyte stimulating hormone and infrared irradiation of the iris in the rabbit eye (IV)

A r ntioned above it ha been est blished in literature that cat cholamines stimulate membrane adenyl cyclase thereby increasing the amount of intracellul r cAMP [57] Interaction between prostaglandins and catecholamines on the adenyl cyclase system of the iris-ciliary tissues h s been reported [7] If the α-MSH effect on the blood aqueous barrier i actually due to its ability to increase the concentration of cAMP [43] [0] one ould expect the adrenergic nervous system to interfere with the α MSH response too This hypothesis was the basis for the present st dy hich present the effect of adrenergic antagonists (α-adrenergic ntagonist phentholamine β adrenergic antagonist propranolol) and adrenergic agoni ts (α adrenergic agonist noradrenaline β adrenergi agonist terbutalin sulfate) on the breakdown of the blood-aqueous barrier elicited by α MSH s compared to pro taglandin and infrared irradiation of the iris The re ults are outlined in Table I

TABLE I

THE EFFECT OF ADRENERGIC ANTAGONISTS AND ADRENERGIC AGONISTS ON THE AQUEOUS FLARE RESPONSE (AFR) TO PGE_2 INFRARED IRRADIATION OF THE IRIS AND α MSH

	α ANTAGONIST phe tol m e ( )	α AGONIST or dr aline (topical)	α ANTAGONIST α AGONIST	β ANTAGONIST propr nol f ( )	β AGONIST erbu ln ulf t (t pic l)	β ANTAGONIS β AGONIST
PGE_2	0	0	t t t d	0	0	t t t d
INFRARED IRRADIATION	-	-	-	-	+	
α MSH	0	+	0	-	+	

0 th AFR wa unaffec d by th d energ g t t t d
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\+ inc d

Adrenergic antagonists Phentholamine and propranolol had no effect on the PGE_2 induced response, while both antagonists reduced the flare response to infrared irradiation The α-MSH response was unaffected by phentholamine while propranolol abolished the α-MSH effects totally

Adrenergic agonists The action of PGE_2 was unaffected both by noradrenaline and terbutalin sulfate Noradrenaline, however inhibited the flare response to infrared irradiation This inhibition might be due to the negative feed back system described to exist between noradrenaline and prostaglandins[9, 18 25]

An alternative explanation may be that the inhibition is due to vasoconstriction of the ciliary vessels thereby counteracting the prostaglandin-induced vasodilatation This vasoconstriction caused by noradrenaline is however probably not strong enough to reduce the vasodilatation and protein leakage induced by the dose of exogenously applied PGE

Noradrenaline increased the aqueous flare response to α MSH

Terbutalin sulfate worked synergistically with both infrared irradiation and α-MSH

Several alternatives for α- and β-adrenergic interaction with prostaglandins have been given in literature[18 22 26] A hypothetical model for the different steps in the course of reactions

in agreement with the present results is suggested in Fig 3

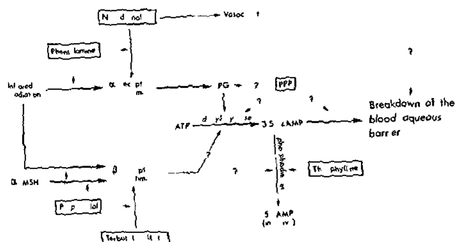


Fig 3 The effect of dr g g th ophylline nd polyphlor nphosphat (PPP) on th br kdown of th bl od aqueou bo ier

The present results indicate that prostaglandins are linked in the inflammatory course one step after the α- and β-receptor stimulation caused by infrared irradiation α MSH seems to exert its effe t on the barrier via β-receptor activity only An effective barrier breakdown could be elicited by infrared irradiation only when both the α-as ell as β adrenergic pathways were intact In conclu-ion it seems a if inta t β adrenergic reception is a prerequisite for barrier breakdown after infrared irradiation - as well as after the non prostaglandin mediated agent α-MSH If this holds true also for prim tes β blockers might have a therapeutical *value in uveitis*

In the present study the pupillary response to PGE_2 and infrared irradiation was also recorded For *infrared irradiation it was* found that phentolamine did not change the immediate pupillary constrict on whereas the pupillary *size* was restored significantly earlier in phentolamin - than in untreated eyes indicating *an inhibi-*tion of prostaglandin activity *Propranolol* caused however a *slight* decrea e of the infrared induced immediate *miosis* he sustained miosis was inhibited totally as was the aqueous flare response

Thus these results further support the suggestion in the first paper that the flare response to infrared irradiation is better correlated to the sustained pupillary constriction reflecting the prostaglandin activity than to the immediate pronounced miosis, which probably mirrors a nervous reflex [45]

3 5 The effect of experimental uveitis on the uptake of PGE_1 in the rabbit iris-ciliary body (V)

It has been reported that PGE_1 is accumulated by the anterior uvea more efficiently than by a number of other tissues [36] This uptake has been shown to take place in the ciliary processes, where in incubation experiments the radioactive prostaglandin or its related metabolites can be detected in the stroma and vessels but not intracellularly in the epithelium [37] It has been suggested that the ciliary epithelium has a detoxifying capacity actively transferring PGE_1 from the interior of the eye to the stroma of the ciliary processes from where the blood stream removes it Bito has shown that the active uptake of ^3H PG is blocked at the peak of experimental uveitis [38] He suggested that this damage to the detoxifying mechanism may be an important factor in the pathogenesis of anterior uveitis In our search for a possible explanation to the action of α-MSH and of topical imidazole on the α-MSH response, we have tested if α-MSH with or without imidazole pretreatment, affects the PGE_1 accumulating capacity of the iris-ciliary body For comparison the prostaglandin uptake after infrared irradiation and after imidazole per se was also tested The aqueous flare response was followed and the rabbits were killed at the expected height of the uveitis The uptake of ^3H PGE_1 in the iris with the ciliary body was then determined The uptake was markedly decreased in the α-MSH treated rabbits in which a severe barrier damage had been recorded When α-MSH caused a more moderate aqueous flare response the prostaglandin uptake on the contrary was significantly increased

Such an increase of the prostaglandin uptake capacity has not previously been reported An inflammatory reaction is consequently not necessarily always the result of a decrease in the prostaglandin uptake and impairment of a hypothetical detoxifying action of the ciliary processes [38] cannot be the only way to elicit an inflammatory response On the contrary it cannot be excluded that the increased prostaglandin accumulation contributes to the barrier damaging effect of α-MSH

Topical imidazole was found to enhance the uptake of prostaglandin after α-MSH treatment correlated to an increased aqueous flare response to α MSH. Topical imidazole per se caused no increase of the PG uptake within 3 hours but after 24 hours a significantly enhanced uptake of prostaglandin was found, though no barrier damage was noticed. In the contralateral eyes the uptake was either slightly but not significantly increased. Imidazole given intraperitoneally had no effect on the accumulation of prostaglandin and caused no aqueous flare increase per se.

The present study indicates that the synergistic effect of topical imidazole and α-MSH may be explained by their similar ability to increase the prostaglandin uptake.

Contrary to α MSH infrared irradiation causing a moderate aqueous flare response did not bring about any significant change in the prostaglandin uptake capacity. Compared to the traumatic agents used by Bito[38] infrared irradiation as used in this study is a weak trauma explaining why damage to the prostaglandin uptake mechanism after irradiation could not be demonstrated. The present results however stress the importance of testing also more moderate stimuli as the eye seems to react differently to the same stimuli at different levels of barrier damage.

3.6 The effect of polyphloretin phosphate on the aqueous flare response to α melanocyte stimulating hormone (VI)

To investigate if PGs actually contribute in some way to the barrier damaging activity of α-MSH though not via enhanced prostaglandin synthesis it was tested if polyphloretin phosphate (PPP) was able to prevent the α MSH effects. PPP has been assumed by Eakins et al[57] to be a selective competitive prostaglandin antagonist.

Subconjunctival PPP. Significant inhibition by subconjunctival PPP was not achieved for PGE_2, PGE_1- or α MSH-induced protein leakage. This is not in line with the results of Bethel and Eakins[16] showing that subconjunctival PPP has a marked blocking effect on the intraocular pressure increase to prostaglandins. However though the intraocular pressure and the aqueous flare response are correlated they are not quite equivalent as parameters of the barrier breakdown which is also reflected in a study by Whitelocke and Eakins. They found that subconjunctival PPP markedly reduced the prostaglandin induced pressure increase whereas the permeability increase to fluorescein in the

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ciliary region was unaffected [53]

Intravenous PPP When given intravenously PPP effectively inhibited the aqueous flare increase caused by PGE_1 or α-MSH, whereas the PGE_2 action was not significantly reduced

Subcutaneous PPP However, when the same dose of PPP was injected subcutaneously instead of intravenously the flare response to all three stimuli was significantly blocked

The present results provide support for two possible suggestions (Fig 3) Assuming that PPP is a specific prostaglandin antagonist the present results support the suggest that prostaglandins take part in the damaging action of α-MSH via pathologically increased prostaglandin accumulation in the iris and ciliary body On the other hand there are studies on other biological systems, indicating that the action of PPP is not due to inhibition at the prostaglandin-receptor level but at a later stage in the course of reactions i e at the adenylcyclase system[54] or even later [55] In that case the present results merely suggest that prostaglandin- and α-MSH effects are mediated via a common factor, possibly cAMP This condition, however, does not preclude the possibility that prostaglandins take part in the barrier damaging effect of α-MSH

3 7 The effect of theophylline on the breakdown of the blood-aqueous barrier in the rabbit eye (VII)

Further experiments were carried out in an attempt to determine the role of cAMP in mediating the barrier effects of prostaglandins and α-MSH Imidazole, which increases cAMP phosphodiesterase activity,[30] had earlier when given generally been shown to antagonize the barrier damage induced by prostaglandin as well as by α-MSH One would expect that agents which, unlike imidazole, inhibit the cAMP phosphodiesterase activity would increase the barrier damaging effect of the different traumatic stimuli, assumed to exert their effect via cAMP Theophylline has phosphodiesterase inhibiting activity[30] and has been used to enhance the accumulation of labelled cAMP for assay of adenyl cyclase activity in ciliary process tissue [22] In the present study the capability of intravenous theophylline to affect the protein leakage induced by α-MSH as compared to prostaglandin and infrared irradiation was tested

Intravenous theophylline significantly promoted the damaging effect of α-MSH on the blood aqueous barrier The aqueous flare response

to PGE_2 and infrared irradiation was also enhanced but the difference in the case of these two stimuli was weak or not significant respectively For PGE_2 the potentiation could be demonstrated when a small do e of PGE_2 causing a modest barrier breakdown was tested When higher doses of PGE_2 were applied theophylline did not contribute to any further increase of the flare response This probably explains why Zink et al [28] failed in demonstrating any effect of aminophylline on the intraocular pressure response to prostaglandin since they tested a dose of prostaglandin which was about twice the highest dose tested in the present study

The test dose of intravenous theophylline per se did not cause any change in the physiological flare but a dose twice the test dose produced a barrier damage in 50 % of the rabbits This protein leakage cau ed by theophylline could not be inhibited by pretreatment of the animals with indomethacin indirectly indicating that an enhanced concentration of intraocular cAMP is able to elicit a barrier disruption without co existing prostaglandin increase

The results also support the earlier hypothesis that cAMP is a common effector of the breakdown of the blood aqueous barrier to different traumatic stimuli whether these are prostaglandin mediated or not (Fig 3)

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It was further shown that polyphloretin phosphate (PPP) known to possess prostaglandin antagonistic action was able markedly to reduce the aqueous flare response to α-MSH as well as to PGE_1 and PGE_2 in agreement with the suggestion that α-MSH and prostaglandins anyhow have a barrier disrupting factor in common (Fig 3)

The interaction of adrenergic agonists and antagonists on the barrier effects of PGE_2 infrared irradiation and α-MSH was investigated (Fig 3) It was found that the prostaglandin action was unaffected by all adrenergic agents tested A barrier breakdown caused by infrared irradiation of the iris could however be induced only when both the α- as well as the β-adrenergic pathways were intact The α-agonist noradrenaline was found to counteract the irradiation effects a condition which may be due to a vasoconstriction in the ciliary vessels but which may also reflect a negative feedback system between noradrenaline and prostaglandins

The action of α MSH seemed to involve only the β-adrenergic system and it was suggested that α MSH stimulates an increased intraocular cAMP concentration via β receptor stimulation

Further support for the hypothesis that cAMP is the common ultimate mechanism which causes the barrier breakdown was achieved in a study of the effects of theophylline on the barrier breakdown Theophylline which contrary to imidazole blocks the inactivation of cAMP (Fig 3) potentiated the protein leakage induced by PGE_2 as well as by α MSH The response to infrared irradiation was also slightly but not significantly increased

In the present investigation the mechanism of the breakdown of the blood-aqueous barrier induced by different irritative stimuli to the rabbit eye was studied

The protein leakage into the anterior chamber (aqueous flare) and the intraocular pressure increase caused by topical prostaglandin E_2 (PGE_2) was recorded parallelly The aqueous flare and intraocular pressure response was found to be correlated to each other, but not to be quite equivalent as parameters of the barrier damage The flare was chosen as the gauge for quantifying the barrier damage througout this investigation

The flare response to PGE_2 but not to its precursor arachidonic acid (AA) could be inhibited by indomethacin, which is known to inhibit the conversion of AA to PGE_2 The protein leakage after infrared irradiation of the iris and intravenous endotoxins was also inhibited by indomethacin, suggesting that these two types of stimuli are prostaglandin mediated The barrier damage induced by subcutaneous α-MSH was not however, reduced by indomethacin and it was claimed that α-MSH causes a barrier breakdown without support of any enhanced prostaglandin synthesis (Fig 1)

The cAMP-phosphodiesterase stimulating agent imidazole was when given systemically able to block the flare response to all the tested stimuli i e to PGE_2 AA infrared irradiation endotoxins and α-MSH Assuming that the imidazole effect is due to its capacity to enhance degradation of cAMP to inactive metabolites, the present results indicate that all the traumatic agents exert their effect via increased intraocular cAMP activity (Fig 2)

However when given topically imidazole was found strongly to facilitate and potentiate the α-MSH response whereas the barrier damage produced by prostaglandin and prostaglandin mediated stimuli was unaffected

α-MSH and topical imidazole were both found to increase the prostaglandin accumulation in the iris- and ciliary body It is proposed that the potentiating synergistic effect of topical imidazole on the α-MSH induced protein leakage may be explained by this similar ability to enhance the prostaglandin uptake Thus it seems as if prostaglandins may anyhow be involved in the barrier damaging effect of α-MSH, despite α-MSH does not cause any increase of the prostaglandin synthesis

It was further shown that polyphloretin phosphate (PPP), known to possess prostaglandin antagonistic action was able markedly to reduce the aqueous flare response to α MSH as well as to PGE_1 and PGE_2 in agreement with the suggestion that α-MSH and prostaglandins anyhow have a barrier disrupting factor in common (Fig 3)

The interaction of adrenergic agonists and antagonists on the barrier effects of PGE_2 infrared irradiation and α-MSH was investigated (Fig 3) It was found that the prostaglandin action was unaffected by all adrenergic agents tested A barrier breakdown caused by infrared irradiation of the iris could, however be induced only when both the α- as well as the β adrenergic pathways were intact The α-agonist noradrenaline was found to counteract the irradiation effects, a condition which may be due to a vasoconstriction in the ciliary vessels but which may also reflect a negative feedback system between noradrenaline and prostaglandins

The action of α-MSH seemed to involve only the β adrenergic system and it was suggested that α-MSH stimulates an increased intraocular cAMP concentration via β receptor stimulation

Further support for the hypothesis that cAMP is the common ultimate mechanism which causes the barrier breakdown was achieved in a study of the effects of theophylline on the barrier breakdown Theophylline which contrary to imidazole blocks the inactivation of cAMP Fig 3) potentiated the protein leakage induced by PGE_2 as well as by α MSH The response to infrared irradiation was also slightly but not significantly increased

4 GENERAL SUMMARY

In the present investigation the mechanism of the breakdown of the blood-aqueous barrier induced by different irritative stimuli to the rabbit eye was studied

The protein leakage into the anterior chamber (aqueous flare) and the intraocular pressure increase caused by topical prostaglandin E_2 (PGE_2) was recorded parallelly The aqueous flare-and intraocular pressure response was found to be correlated to each other, but not to be quite equivalent as parameters of the barrier damage The flare was chosen as the gauge for quantifying the barrier damage througout this investigation

The flare response to PGE_2 but not to its precursor arachidonic acid (AA) could be inhibited by indomethacin, which is known to inhibit the conversion of AA to PGE_2 The protein leakage after infrared irradiation of the iris and intravenous endotoxins was also inhibited by indomethacin, suggesting that these two types of stimuli are prostaglandin mediated The barrier damage induced by subcutaneous α-MSH was not, however, reduced by indomethacin and it was claimed that α-MSH causes a barrier breakdown without support of any enhanced prostaglandin synthesis (Fig 1)

The cAMP-phosphodiesterase stimulating agent imidazole was when given systemically able to block the flare response to all the tested stimuli i e to PGE_2, AA infrared irradiation endotoxins and α-MSH Assuming that the imidazole effect is due to its capacity to enhance degradation of cAMP to inactive metabolites, the present results indicate that all the traumatic agents exert their effect via increased intraocular cAMP activity (Fig 2)

However, when given topically imidazole was found strongly to facilitate and potentiate the α-MSH response whereas the barrier damage produced by prostaglandin and prostaglandin mediated stimuli was unaffected

α-MSH and topical imidazole were both found to increase the prostaglandin accumulation in the iris- and ciliary body It was proposed that the potentiating synergistic effect of topical imidazole on the α-MSH induced protein leakage may be explained by this similar ability to enhance the prostaglandin uptake Thus it seems as if prostaglandins may anyhow be involved in the barrier damaging effect of α-MSH, despite α-MSH does not cause any increase of the prostaglandin synthesis

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The vignett is a drawing by John Tenniel (From Alice s Adventures in Wonderland by Lewis Carroll)

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SUPPLEMENTUM 129

A K. K. K. LUNDSGAARD EDI COEPTA

Optic Disc Drusen in Children

by

Heikki Erkkila

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INTRODUCTION

In the anomaly of the optic nerve head known as optic disc drusen the pathognomonic sign is the presence of round light reflecting excrescences on the optic disc This well recognized appearance of the optic disc is preceded in children by an anomalously elevated condition of the disc without superficial concrements (Braun 1935) In 1958 *François and Verriest reviewed all the available reports of optic disc* drusen Their analysis showed that elevation of the optic disc with deeply situated drusen was a preliminary *mostly prepubertal stage* of the anomaly Today any anomaly of the optic disc attributable to buried drusen on the basis of the ophthalmoscopic picture and/or familial occurrence is classified among optic discs with drusen (Walsh and Hoyt 1969) The anomaly is determined by an autosomal gene and shows an irregularly dominant mode of inheritance (Lorentzen 1966)

In children the anomalous discs cause problems in the differential diagnosis of papilloedema According to Fotzsch (1969) this is because the drusen are still buried In the histopathological series of Friedman et al (1975) both superficial and buried drusen were seen in optic discs of patients between 43 and 76 years of age The previous reports on optic disc drusen comprise about 600 cases, of which less than 100 were stated to be in subjects under 15 years of age (see Table 1)

In all congenital anomalies the earlier the diagnosis the better For when the anomaly is expected to cause complications early diagnosis often allows effective prophylaxis Another advantage is that early recognition of the anomaly may often save the patient from the extended examination procedures required for differential diagnosis between the anomaly and acquired diseases In drusen of the optic disc the latter aspect is extremely important. As there had been no systematic evaluation of optic disc drusen in relation to growth and development a study was indicated on the occurrence the clinical appearance and the neurodevelopmental aspects of the anomaly in children.

Historical survey of clinical aspects

After the first histopathological (Muller 1858) and ophthalmoscopic (Liebreich 1868) reports on spherical concrements in the optic nerve head this condition was believed to be associated with drusen of the lamina vitrea It was Hirschberg and Cirincione (1891) who first clearly delimited drusen of the optic disc as an ophthalmological condition Most of the patients cited in the early reports were adults, but in 1878 Nieden presented a case in a girl of 14, and called the concrements drusen During the follow up of this patient Nieden (1889) observed that the drusen multiplied Since Nieden s investigations the name drusen has been used generally for the condition Drusen is a term used in mineralogy for cavities lined with crystals (Wahrig 1975)
Lauber (1907) was the first to demonstrate that optic disc drusen is a hereditary condition One of his patients was a girl of 15 in whom optic disc drusen had been seen one year previously Additionally, drusen were present in the optic discs of her mother and elder sister From his study Lauber concluded that optic disc drusen is a hereditary anomaly of development which can be observed even in the very young
Lauber's views later gained strong support from Braun (1935), who suggested a dominant mode of inheritance Braun s series comprised considerably more children and adolescents than any of the previous investigations and he in particular emphasized the developmental aspects of the anomaly He presented some young individuals with considerable elevation of the optic discs but without ophthalmoscopically distinguishable concrements In the families of these young individuals, many of the older members had conspicuous disc drusen During follow up many of the anomalously elevated optic discs later showed clearly visible drusen
François and Verriest collected the observations of optic disc drusen reported up to 1958 The series were divided into three categories the first comprising patients with acquired aye diseases the second those with heredodegenerations and the third those without any bulbar or optic nerve disease apart from disc drusen The last named category

TABLE I

Cases gathered *from the literature* subjects under 15 years of age with optic disc drusen

Author	Sex and age	Symptoms	Additional diagnoses
Nieden (1878)	F 14	headache hemeralopia	retinitis pigmentosa
Schafer (1884)	F 13		*iridochoroiditis suppurativa*
Gifford (1895)	F 11		*haemorrhage of the vitreous*
Streiff (1904)	F 14	obscurations of vision	strabismus convergens
Lauber (1907)	F 14		
Walker (1915)	M 13		retinitis pigmentosa
Plummer (1935)	M 10	*asthenopia*	*hyperopia*
Braun (1935)	F 13 *2 M 12 4*		
Biernacka Biesiekierska *and Wieczorek (1935)*	M 13		taperoretinal degeneration
Leimgruber (1936)	F 13 3 M 13 13 6		
Reese (1940)	M 12	headance vomiting, disturbance of vision	haemorrhage of the optic disc and the vitreous body
François (1949)	F 12	headache	
Chambers and Walsh (1951)	F 7		
Chavanne and Moreau *(1952)*	M 13	headache blurring of *vision vomiting*	
Callais (1952)	F 11	headache fever	peripapillary haemorrhage
Brégeat (1956)	F 8 M 11	*convulsions*	
Mosci (1956)	F 12		retinitis pigmento a deaf mute
François et al *(1956)*	*F 12*		
Walsh (1957)	9		taperoretinal degeneration
Buraczewski (1958)	2 F 14 6		tapetoretinal degeneration
Pietruschka (1959)	M 6		retinal heredodegeneration
Forsius and Eriksson *(1961)*	M 11		
Algan and Guilemin *(1962)*	F 10		*meningo-encephalitis*
Forsius et al (1962)	M 13		x linked hereditary retinoschisis
Hoyt and Pont (1962)	10 M 4–12 F 10	7/10 convulsions	
Pollack and Becker (1962)	F 13	convulsions	
Catros et al. (1963)	F 10	diplopia paresis of lower extremities	
Brun (1963)	F 13 2 M 14 14	1/2 headache	
Lorentzen (1966)	13 F 8	momentary visual failure	
Stanka (1966)	*M* 6 F 5		
Rutkowska and Merz (1969)	F 14	headache lo *s of* consciousness	
Blair and Walsh (1969)	M 9	headache	
Walsh and Hoyt (1969)	*M 7*	headache vomiting obscurations of vision *truncal ataxia*	medulloblastoma
Calkins (1970)	M 15		repeated peripapillary subretinal *heamorrhages*
Fotzsch (1970)	3 M 10 10 12 2 F 13 14	*1/3 headache* *1/1 headache 1/1 blurred* vision syncope	

Garston and Strachan (1970)	F 13		retinitis pigmentosa
	M 10		retinitis pigmentosa
Maumenee (1970)	2 <15		Bergmeister s papilla
			haemorrhagic detachment of the macula
Otradovec and Vladyková (1970)	F 8		
Cohen (1971)	F 14	headache	peripapillary heamorrhage
Sanders et al (1970)	2 M 9 12	headache	
Forsius et al (1971)	M 7	1/2 blurred vision	1/2 subretinal haemorrhage
Gilson et al (1971)	F 14		grouped pigments retina
Henkind et al (1972)	2 F 6 10	headache	
		deterioration of vision	haemorrhages (2/2 subretinal, sub pigment epithelial and 1/2 on the disc)
Karel et al (1972)	M 13	shadow in front of the eye	peripapillary haemorrhages
Krill et al (1973)	M 8		pseudoxanthoma elasticum
Pietruschka and Priess (1973)	8 <10		
Wise et al (1974)	F 11	deterioration of vision	haemorrhages (peripapillary sub pigment epithelial, subretinal and on the disc)

also called idiopathic drusen, they analysed in detail In this category *only 4 out of 150* patients were under 10 years of age As regards visual function, the most important disability caused by optic disc drusen was considered to be due to the slowly progressing visual field defects resembling those occurring in glaucoma In their analysis they divided the drusen into two types external and internal, corresponding to superficial and buried drusen Their study also concerned the neurological disorders which were found in more than one fourth of the individuals with idiopathic drusen

Lorentzen's (1966) comprehensive study on disc drusen included his own series of 70 patients and an evaluation of the genetic aspects based on ophthalmoscopy of the patients relatives Furthermore Lorentzen gave an estimate of the frequency of disc drusen in Denmark His own series *included only patients with ophthalmoscopically visible round light* reflecting excrescences on one or both discs The drusen were seen most frequently in the nasal quadrants of the optic discs In these areas the contour of the disc was most diffuse The visual field defects seen in more than three fourths of Lorentzen s patients were most frequent in the lower nasal and lower temporal quadrants Ophthalmoscopies performed on patients relatives confirmed François and Verriest s (1958) view of an irregularly dominant mode of inheritance

Lorentzen evaluated the frequency of optic disc drusen at 3 4 per thousand a figure based on 11 cases found among 3 200 patients in his ophthalmological practice In his own series the mean age of the patients was 40 years, the youngest being 13 years of age The genetic study did not include individuals under 8 year

Of the 66 patients of the series presented by Pietruschka and Priess (1973) 8 were under 10 years of age but the features of the anomaly were not studied in relation to age Many of the patients were followed up for more than 5 years some of them for more than 10 years The follow up records include only observations on visual function In this respect more than half the patients showed no progression In those in whom visual function deteriorated during the follow up progression was considered slight

Differential diagnosis

Elevation of the optic nerve head due to concrements anterior to the lamina cribrosa was mentioned by Muller as long ago as 1858 The gross examination after the opening of the bulb made by Iwanoff (1868) suggested choked disc As regards ophthalmoscopic examinations Hirschberg and Cirincione (1891) presented cases in which the anomaly had been mistakenly interpreted as optic neuritis or papilloedema

The importance of optic disc drusen in the differential diagnosis of papilloedema was emphasized by Hoyt and Pont (1962) Their series consisted of 28 patients with anomalous elevation of one or both discs, which had been taken for papilloedema. Most of the patients were young The diagnosis of disc drusen was made in 25 out of 28 individuals Only five individuals presented glistening granules on the elevated discs In the others Hoyt and Pont made a diagnosis of buried drusen The diagnosis was supported by at least one of the following findings (1) a hard amorphous appearance of the optic disc elevations (2) irregular elevated disc margins (3) transillumination of the elevated disc tissue with oblique ophthalmoscopic illumination or with the beam of the slit lamp (4) the presence of drusen in the other eye or in the eye of a family member

Fotzsch s (1970) series comprised 30 patients in whom optic disc drusen resembled true papilloedema The age distribution of this series shows an accumulation between the ages of 10 and 19 years which Fotzsch attributed to the age-correlated variation of the visibility of the drusen However the series included no patients under 10 years of age

In fluorescein angiography disc drusen present several characteristics which are of great importance in the differential diagnosis of papilloedema (Miller et al 1965 Sanders and ffytche 1967 Blair and Walsh 1969 Dufour et al. 1971 Hayreh 1974) Apart from the actual angiographic features disc drusen also display a peculiar autofluorescence In a comment on one of my own investigations Henkind (1975) suggests ultrasonography as a method of examination in patients with suspected optic disc drusen.

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My aims in the present study were
- to assess the prevalence of optic disc drusen from a sample of a population of children
- to form an opinion on the clinical appearance of disc drusen in childhood and
- to throw light on the accompanying neurodevelopmental aspects of the disorder

The results of my own investigations have been presented in detail in the following four communications which together with this survey are here presented as a doctoral thesis

I Erkkila H Optic disc drusen in children Albrecht v Graefes *Arch klin exp Ophthal* 189 1–7 (1974)

II Erkkila H Clinical appearance of optic disc drusen in children Albrecht v Graefes Arch klin exp Ophthal 193 1–18 (1975)

III Erkkila H The central vascular pattern of the eyeground in children with drusen of the optic disk Albrecht v Graefes Arch klin exp Ophthal 199 1–10 (1976)

IV Santavuori P and Erkkila H Neurological and developmental findings in children with optic disc drusen Neuropadiatrie 7 283–301 (1976)

These articles will be referred to in the text by their Roman numerals I–IV

SUBJECTS AND METHODS

In an endeavour to investigate the occurrence of drusen of the optic disc in an almost unselected sample of Helsinki children, a total of 1 0 6 children was studied (I) These children were examined in autumn 19 2 soon after they had started school in the Helsinki municipal primary schools The majority reached the age of 7 during that year Thirty seven classes were examined consecutively The sample was considered representative of the total number of 6 477 Form I pupils in Helsinki municipal primary schools

In each child both optic discs were examined at the schools with the Heine ophthalmoscope and a semicircular beam of light Anomalous optic disc elevation even in the absence of visible superficial hyaline concrements was taken to be an optic disc with

Pathogenesis and complications

Regarding the origin and genesis of the drusen of the optic nerve head there is no consensus Reese (1940) believed that these excrescences are produced by degeneration of excess of immature neuroglia Cibis (1940), in his histological specimens of disc drusen found alterations in the vessel walls of the disc Seitz and Kersting (1962) believed that the drusen are derived from degeneration of the axoplasm Kurus and Kurus (1973) regard drusen and other deposits in the region of the eye and optic nerve as a result of dyscolloidosis

The visual field defects are considered to be the result of damage to the nerve fibres caused by drusen lying adjacent to the lamina cribrosa and sclera (Walsh and Hoyt 1969) In some cases, according to Hayreh (1974) pressure in the disc by drusen may produce local circulatory disturbances for example, localized ischaemic optic neuropathy with oedema (leading, later on, to atrophy in that region), superficial or deep retinal haemorrhages on the disc or peripapillary areas, retinal venous stasis and development of retinociliary veins on the disc

In recent years many of the reports on disc drusen concern the haemorrhagic complications (Otradovec and Vladyková 1970, Sanders et al 1970 1971 Gilson et al 1971, Henkind et al 1972 Karel et al 1972 Thomas et al 1972 Brodrick 1973, Wise et al 1974) These series include several children In addition, retinal haemorrhages in children with optic disc drusen have been reported by Reese (1940) Gallais (1952), Brégeat (1956), Calkins (1970) and Maumenee (1970) Haemorrhages were also found in the histopathological series of Friedman et al (1975)

Optic disc drusen in children

Eighty three subjects under 15 years of age with disc drusen who were reported by other authors are listed in Table I The list is not complete for instance, reports of cases in the South American literature were not available In addition, the series of Lorentzen (1966) Hoyt et al (1962) and Pietruschka and Priess (1973) included subjects whose ages were given as between 10 and 20 years without more precise information I am aware of no previous investigations particularly concerned with disc drusen in children

included in the series as are the two cases discovered by ophthalmoscopy in relatives of the subjects The fundi of 85 members of the subjects families were examined and optic disc drusen were found in 12 members i e 6 mothers 2 fathers 2 brothers and 2 sisters
In addition to ophthalmoscopy the ophthalmological examination made at the clinic included testing of vision with Snellen charts inspection of the eyes testing of the eye movements and pupillary responses biomicroscopy of the anterior parts of the eyes and refractoscopy Biomicroscopy was performed with a Haag Streit 900 slit lamp and refraction was determined during cycloplegia with a streak refractoscope
The visual fields of 48 subjects were examined with a Friedmann central visual field analyser or a Goldmann perimeter The two subjects who were not examined were both under 6 years of age. In addition the retina surrounding the disc was examined as far as the midperiphery with a Heine ophthalmoscope in both eyes under cycloplegia In the fundi of all the subjects the area of the optic nerve head was photographed with a Zeiss fundus camera on Agfachrome 1000 S colour reversal film
In 24 subjects the intraocular tension was measured with a Schiotz tonometer or an applanation tonometer
The vascular pattern of the optic disc area was further studied in fundus photographs of the 50 children examined clinically Colour transparencies of all the 92 optic discs with drusen were used for a qualitative analysis of the fundal vessels in the optic disc area. The qualitative analysis concerned the source and configuration of the aberrant vessels. The colour transparencies of all the 46 right sided optic discs were used for a quantitative analysis of the vascular features The quantitative analysis dealt with measurements of three variables on magnified projections of the transparencies These measurements were made with an arrangement similar to that presented by Forsius et al. (1964) The colour transparencies were projected on the glass screen of a mirror projector Porst Visomat TL 12 The three variables measured were N (number) L (length) and T (tortuosity) N being the number of vessels crossing a peripapillary counting circle *(Fig 1)* A similar counting method was used by Kagan et al. (1967) L is the length of the superior and inferior branches of the central retinal vein and artery measured with a map measurer between the respective second branching points T is a measure of the tortuosity expressed as a ratio the sum of the measured lengths of the eight largest vessels between two counting circles divided by the sum of the corresponding radial lengths This method is a modification of the estimation of tortuosity presented by Irinoda (1970) The method used for investigation of the vascular features is described in detail in III
For the vascular findings a control series was used which comprised 46 consecutive subjects aged 4—15 years treated in the strabismus out-patient clinic of Helsinki University Eye Hospital. In the controls the optic disc area of the better eye was photographed by the same procedure as in the subjects with drusen.
Another control series comprising the right or left optic discs of ten children or young adults with true papilloedema was included in the quantitative analysis of the vascular features studied (variables N and T)
The origins of some vessels and the choroidal vascular pattern around the optic discs with drusen were studied by fluorescein angiography in 32 eyes of 28 subjects. Fluorescein angiography was performed with 5 cm^3 of 10 % sodium fluorescein injected intravenously into an antecubital vein. Angiography was started 6 s after injection with a modified Zeiss Robot fundus camera A Baird Atomic B 4 interference filter was employed as the excitation filter and the barrier filter was a Kodak Wratten 15 The film used was Kodak Tri-X Pan.
Each of the 50 children with optic disc drusen underwent a neurological examination according to the standardized procedure developed by the neuropaediatric department of the Children s Hospital, University of Helsinki (IV). In addition to the physical examination, an electro-encephalogram (EEG) was recorded in all children. The EEGs

drusen when the elevation had a hard amorphous appearance or the disc margins were irregular and elevated when transillumination of the elevated optic disc tissue was produced by indirect ophthalmoscopic illumination or when drusen were found in the subject s contralateral eye or in the eye of another member of the family (cf Hoyt and Pont 1962)

The children with optic disc drusen detected in this mass screening were re-examined in detail by the author at the Eye Clinic of Helsinki University Central Hospital The ophthalmological examination was performed in the same way as for the series of 50 children studied in an attempt to investigate the clinical appearance of optic disc drusen in childhood (II and III) This series of 50 subjects under 15 years of age includes nearly all the cases of optic disc drusen diagnosed in the children seen at Helsinki University Eye Hospital in 1971—1974 The four probands found in the screening of schoolchildren are

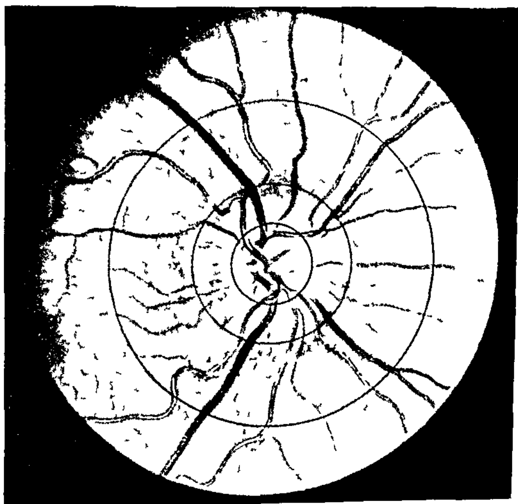


Fig 1 *Counting circles drawn on a fundus photograph (the right eye of case 42) with radii of the same relative lengths as used for the measurements of the variables N (number of vessels crossing the intermediate counting circle) L (summed length of the primary branches of the central retinal vein and artery) and T (tortuosity expressed as a ratio the sum of the measured lengths of the eight largest vessels between the innermost and outermost counting circles divided by the sum of the corresponding radial lengths)* (Reproduced by courtesy of the editor of *Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie)*

1 Frequency

Among the 1 076 Form I pupils (573 boys and 503 girls) examined at Helsinki municipal primary schools four (three boys and one girl) were found to have anomalous elevation of the optic disc attributable to buried drusen (Fig 2) The 90 per cent confidence limits for the prevalence of optic disc drusen in the series studied are 1 and 7 per 1 000 obtained with the Poisson distribution

2 Ophthalmological appearance (see also Table II)

Optic disc

Drusen were diagnosed in both optic discs of all but 8 of the 50 children of the clinical series

Superficial drusen were seen in 12 children in 3 of them in both discs In 30 children buried drusen were diagnosed bilaterally In those eight children in whom the anomaly was considered unilateral only buried drusen were diagnosed Discs with superficial and buried drusen did not appear to differ in any other features seen by ophthalmoscopy All the discs with superficial drusen showed an anomalous elevation equal to that seen in those with buried drusen

The height of the elevation was not measured but its extent was determined as the proportion of the disc margin affected In 40 discs the elevation comprised the whole circumference In ten children this condition was bilateral In the remaining 52 discs elevation was partial in these discs the elevation mostly affected the nasal part and with few exceptions the elevated part of the margin comprised at least 180° of the disc circumference In some of the discs with partial elevation a slight physiological cup was seen. Nearly all the discs with drusen had a narrow vascular funnel even when the entire circumference was elevated.

In addition to the ten children with bilateral total elevation at the disc margins there was one child in whom partial elevation was regarded as symmetrical in the two discs Thus in 39 of the children studied the distribution of the drusen was asymmetrical

were taken at the Children s Hospital with an 8-channel Elema apparatus The electrodes were silver silver chloride discs placed in relation to bony landmarks (Pampiglione 1956) and fastened with a net EEGs were taken in 12 patients in both the waking and the sleeping states and in 38 during the waking state only In every subject tests were made on the effects of voluntary hyperventilation and photic stimulation The radiological examinations included skull X rays of all the subjects In addition the left hand was radiographed in 38 children for estimation of skeletal age by reference to Greulich and Pyle s Atlas (1950) Eight subjects underwent pneumoencephalography Carotid angiography was performed in nine subjects in three of them on both hemispheres In nine subjects routine examination of the cerebrospinal fluid was performed including cell counting and determinations of total proteins and glucose concentrations The indication for these studies was suspicion of intracranial abnormality

Weight height and head circumference were measured at least once in every subject. The parents of the children were interviewed concerning the pre and perinatal history rate of development and school performance of the children and the diseases that had occurred in the children and their relatives In this interview special importance was attached to eliciting the subjective symptoms or other reasons which led the parents to seek medical advice

Statistical methods

The confidence limits for the prevalence of optic disc drusen found during the mass screening of schoolchildren were computed with the Poisson distribution

For testing the significance of the difference in the frequency of superficial drusen and visual field defects in two age groups of the series studied and in the frequency of a cilioretinal artery in the series studied and the control group the chi square test was used Student s t test was used in the quantitative analysis of the continuous variables measured on the fundus photographs

Vascular features of the central eye ground

A qualitative analysis was made of the aberrant vessels of all 92 optic discs with drusen this was supplemented with a quantitative analysis of the course and branching of the major central retinal vessels Variables characterizing these two features were measured on the fundus photographs of the 46 right sided eyes with disc drusen In addition the fluorescein angiograms made on 32 eyes were studied to determine the peripapillary choroidal pattern and the origin of the aberrant vessels seen by ophthalmoscopy in 4 children.

In 40 of the 92 eyes with disc drusen a cilioretinal artery was present in 20 right sided and in 20 left sided Nine subjects had the two conditions bilaterally and in one subject a cilioretinal artery was present bilaterally but drusen were diagnosed in only one eye Twenty two subjects had a cilioretinal artery in one eye with optic disc drusen

In 18 of the 20 right sided fundi having a cilioretinal artery associated with disc drusen the vessel emerged at the temporal circumference of the disc in one of them the artery was double (case 47) In two subjects the artery was a nasal vessel Most of the 20 cilioretinal vessels of the right sided fundi with drusen were small but in two fundi the vessel fed a sector occupying more than a fifth of the entire peripapillary circumference In the control group a single cilioretinal artery was seen in 11 of the 46 fundi in all of them at the temporal circumference of the disc. All these 11 arteries supplied a sector covering less than a fifth of the entire peripapillary circumference

In 4 of the 92 eyes with drusen small tortuous aberrant vessels were seen on the optic discs All these cases (11 22 38 and 48) were unilateral and the subjects were submitted to fluorescein angiography The aberrant vessels were identified as veins draining outside the main retinal venous trunk.

In 1 (case 12) of the 92 eyes with disc drusen a remnant of the hyaloid artery was found. In all but one of the fundi with disc drusen the central retinal vessels branched dichotomously in the exeptional eye (case 45) the inferior retinal artery branched trichotomously In two eyes (cases 16 and 34) with disc drusen one of the temporal secondary branches of the central retinal artery was seen to cross the horizontal radius between the disc and the macula In the control series this condition was not present in any of the fundi, neither were there any remnants of the hyaloid artery tortuous disc vessels or trichotomous branchings

The quantitative analysis of the central retinal vessels of the 46 right sided fundi with optic disc drusen was made on the basis of variables measured on the fundus photographs In the series studied the variable N which expresses the number of vessels crossing the peripapillary



Fig 2 Optic discs with buried drusen in a boy aged 7 (case 6) found during mass screening of schoolchildren.
(Reproduced by courtesy of the editor of *Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie)*

The affected discs were frequently of an unusual, greyish colour, like marble The abnormal colour was most evident at the highest parts of the elevations and near the disc margins Superficial drusen were distinguishable as sharply defined areas lighter in colour than their surroundings when viewed under direct illumination or in photographs Two children (cases 18 and 20) had small darkly pigmented dots in the upper parts of the optic discs in one of these subjects the dots were seen bilaterally

The affected discs had irregular margins The irregularity, which varied in degree, was due to protuberances projecting from the margins towards the surrounding retina like small semi lunar adnexa In one of the subjects the irregularity of the optic disc margins was extremely pronounced (case 31)

In the 15 discs in which superficial drusen could be seen, the number ranged from 1 to 6 with an average of 2 5 The superficial drusen observed were spherical, with a diameter not exceeding the breadth of a superior or inferior papillary vein In most of the drusen the diameter roughly equalled the breadth of a secondary branch of the central retinal artery The superficial drusen were frequently situated close to the nasal margins of the optic discs or in the vicinity of vessels If there were more than three drusen, they tended to form clusters

Buried drusen that were invisible in direct ophthalmoscopic illumination could often be seen in the oblique illumination given by the semicircular light beam of the ophthalmoscope This applied in particular to the small protuberances at the disc margins, but the glow produced by buried drusen in oblique illumination was also frequently seen in the areas of the discs adjacent to the central vessels

counting circle ranged between 15 and 24 vessels with an average of about 19 vessels In the control group consisting of the »better eyes of 46 strabismic children the range was 12–21 vessels averaging about 16 vessels The other control group comprising one of the eyes of ten children or young adults with true papilloedema showed a range of 13–18 vessels on the counting circle with an average of about 16 vessels

In the drusen series the values of the variable L indicating the summed length of the two main branches of the central retinal artery and vein proximally to the second branching points ranged between 0 and 40 units. In a high proportion of the fundi the length of the primary branches was considered to be 0 because the artery emerged as four vessels of second degree and there was no visible union between the veins of second degree that form the superior and inferior papillary veins The average summed length of the central retinal vessels of first degree was about 12 units In the control series the summed length of the first branches varied between 0 and 40 units averaging 16 units

The course of the peripapillary vessels is characterized by the variable T a ratio calculated from the lengths of the vessels between two counting circles and used to express the tortuosity In the series of children with disc drusen the T values had a range of 1 04 1 31 with an average of 1 13 In the control group with strabismus the range was 1 04 1 17 the average 1 09 In the other control group with true papilloedema the range of T values was 1 04 1 15 with an average of 1 09

The peripapillary choroidal vascular pattern was studied by fluorescein angiography The findings were classified with respect to the filling sequence of the choriocapillaris in the peripapillary area Four of the 32 angiograms taken in the eyes with optic disc drusen were too difficult to evaluate Six angiograms showed even filling of the peripapillary choriocapillaris In three of them filling was completed before the retinal arterial phase in one during the arterial phase in the other two only after the beginning of the venous phase In 22 angiograms filling of the choriocapillaris was uneven In twelve of them the area of delayed dye filling disappeared before the retinal venous phase of angiography In the remaining ten angiograms the area of delay could still be seen after the retinal venous phase had begun In 15 angiograms the area of delay in the peripapillary choriocapillaris was sectoral and in seven of them it could still be seen at the retinal venous phase In another seven angiograms the mode of delay was circumpapillary and in three of them it was still visible at the retinal venous phase

In 13 of the 15 angiograms with sectoral underfilling the area of delay was in the lower parts of the peripapillary choroid

TABLE II

Summary of the findings in the children of the present series

case	sex and age		type of drusen right	type of drusen left	field defects right	field defects left	neurol signs	EEG abnorm	presenting symptom	developmental disorders
1	M	4	–	B	–	–	–	–	headache seizures	+
2	M	4	B	B	not examined		±	–	headache vomiting	
3	M	5	B	B	–	–	+	–	head tilting	
4	M	5	B	–	not examined		+	+	vomiting	
5	F	7	B	B	–	–	+	+	vomiting	
6	M	7	B	B	–	–	++	–	–*	
7	F	7	B	B	–	–	–	+	seizures	
8	F	7	B	B	–	–	–	+	headache vomiting	
9	M	7	B	B	–	–	–	±	blinking of eyes	
10	F	7	B	B	–	–	±	+	skull abnormality	
11	F	8	B	B	–	–	+	±	squint	
12	F	8	B	B	–	–	±	–	blinking of eyes	+
13	F	8	–	B	+	+	+	+	–*	+
14	M	8	B	B	–	–	+	–	–*	
15	M	8	B	B	+	–	++	–	speech difficulties	+
16	M	8	S	B	–	–	+	±	itching of the eyelids	
17	M	8	B	B	–	–	+	–	seizures	+
18	M	8	B	B	–	–	+	–	–*	+
19	M	8	B	–	–	–	+	±	alteration of character	+
20	F	9	B	B	–	–	+	±	headache	
21	F	9	B	–	–	–	–	–	headache	
22	F	9	B	B	–	–	+	+	headache	+
23	M	9	B	B	–	–	–	+	headache vomiting	
24	F	9	B	S	–	–	–	+	precocious puberty	+
25	F	9	S	B	–	–	–	+	seizures	+
26	F	9	B	S	–	–	–	–	–**	
27	F	9	B	B	–	–	–	–	headache	
28	M	10	B	B	–	–	–	–	headache vomiting	
29	M	10	S	B	–	–	–	–	restlessness during sleep	
30	M	10	B	B	–	–	±	–	*dyslexia*	+
31	F	10	B	B	+	–	–	+	seizures	+
32	F	11	B	B	–	–	+	+	seizures	
33	M	11	–	B	–	+	–	–	squint	
34	M	11	B	B	–	–	–	+	seizures	
35	M	12	B	B	–	+	+	+	headache vertigo	+
36	F	13	B	–	–	–	–	+	poor sight	
37	F	13	B	B	–	–	–	+	seizures	
38	F	13	B	S	–	+	+	–	squint	+
39	M	13	B	S	–	–	–	+	headache	+
40	M	13	B	B	–	+	++	–	mental retardation	+
41	F	13	B	B	–	–	–	–	poor sight	+
42	M	13	S	S	–	–	+	+	squint	
43	M	14	B	B	–	–	–	+	–**	
44	F	14	–	B	–	–	±	+	headache	
45	F	14	S	S	–	–	+	+	soreness of eyes	+
46	M	14	S	S	+	–	–	+	numbness in leg	
47	M	14	B	B	–	–	–	+	seizures	+
48	F	14	B	S	–	–	–	–	headache	
49	F	14	B	B	–	–	–	–	seizures	+
50	F	14	S	B	+	+	–	–	dimness of vision	+

B = anomalous elevation of the optic attributable to buried drusen
S = superficial drusen on the disc
* = *ascertained at screening*
** = sibling of patient

most clearly at the temporal approach to the cornea In another subject (case 11) the corneal endothelium showed a thin opacity resembling a column of type-written parentheses In a third subject, one eye had a small subepithelial macula of the corneal stroma suggestive of complication after a foreign body
None of the subjects studied had conjunctival abnormalities
In all the eyes with disc drusen biomicroscopy showed that the iris was normal in structure In the great majority of the children studied the colour of the iris was blue only three children had brown irises In this respect the sample does not appear to differ from the general population of Finland (Forsius et al. 1970) No heterochromia iridis was recorded

Motor functions

All the subjects examined had pupils of equal size and the pupillomotorics were considered normal
No definite limitations of eye movement were observed in any of the children studied End position nystagmus was diagnosed in seven in three of them (cases 1 22 and 26) it was asymmetrical
The cover test revealed manifest strabismus in five (cases 10 11 17 33 and 47) three of these had unilateral esotropia and two (cases 10 and 47) exotropia associated with the V syndrome In addition heterophoria was diagnosed in five in three of them with eso- and in two with exodeviation

Eyelids and orbits

Five of the children studied (cases 1 3 12 18 and 28) had symmetrical epicanthus in most of them the anomaly was slight. In three children (cases 30 32 and 45) the palpebral fissures were unusually narrow in two of them the narrowness was symmetrical. One subject (case 32) had slight unilateral ptosis In two children (cases 2 and 10) a facial anomaly involving hypertelorism was present

Refraction

Of the 92 eyes with optic disc drusen 61 had a refractive error within the range of −0 25 to +1 75 D and astigmatism of less than 0 75 D In 16 eyes of 13 subjects astigmatism was 0 75 D or more. Myopia of 0 5 D or more was found in 11 of the non astigmatic eyes and as the spherical equivalent in two astigmatic eyes Hyperopia of 2 D or more was observed in four non astigmatic eyes and as the spherical equivalent in another four astigmatic eyes.
Three subjects had anisometropia of 1 5 D or more In one subject (case 33) this condition was associated with amblyopia

Retina

In one (case 41) of the children studied, a small well demarcated accumulation of pigment attributable to retinal naevus was seen in the left eye ground above the macula In the remaining 91 eyes with disc drusen the central retina was considered normal except for the vascular findings reported above

As a consequence of the elevation of the optic disc, a sharp edged, bright ring of reflected light, also visible in photographs is seen in ophthalmoscopy at a distance from the disc centre approximately equal to the disc diameter Within this ring the retina round the optic disc appears to have abnormally dark pigmentation This, however, is an artifact due to the reflection of light In 15 of the 92 eyes with disc drusen the retinal pigmentation in the near and mid periphery was considered unusually thin Otherwise no acquired or degenerative changes of the retina could be seen in any of the eyes studied

Vitreous body

As reported above, one of the eyes of one child (case 12) with disc drusen had a vascular structure identified as a remnant of the hyaloid artery In another child (case 32), one of the eyes had a minute peripapillary membrane This can also be considered a remnant of the embryonic structures No opacities suggestive of inflammatory or degenerative processes were seen in any of the children

Lens

One subject (case 33) had a thin circular opacity unilaterally on the anterior surface of the lens No lental abnormalities were discovered in the other subjects

Anterior chamber and intraocular tension

Biomicroscopy of the anterior chambers of the eyes with disc drusen revealed no structural abnormalities in any of the subjects The aqueous humour was also found to be normal in all the eyes studied In the 24 subjects examined tonometrically the intraocular tension was between 11 and 22 mmHg The measurements showed no asymmetry in subjects with drusen bilaterally, or in those few cases examined in which the anomaly was diagnosed unilaterally In eyes with disc drusen the average intraocular tension was 16 5 mmHg

Cornea, conjunctiva and iris

In one subject (case 49) with optic disc drusen biomicroscopy of the anterior parts of the eyes revealed partial embryotoxon in one eye seen

most clearly at the temporal approach to the cornea In another subject (case 11) the corneal endothelium showed a thin opacity resembling a column of type-written parentheses In a third subject one eye had a small subepithelial macula of the corneal stroma suggestive of complication after a foreign body

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l acuity, tested separately in both eyes with Snellen charts, was to be 1 0 or better in 43 of the children of the series In three cases 7 and 33) a visual acuity of less than 1 0 was combined with :ular esotropia, in one of them (case 33) this was associated with 'erable anisometropia, in another (case 11), with unilateral iatism In one subject (case 19) a subjective estimate of visual was unobtainable because of behavioural alteration Three other :ts in whom visual acuity of 1 0 or better could not be recorded for yes were under 6 years of age

of the 89 eyes with disc drusen the visual fields were regarded as l In the remaining 10 eyes there was a field defect. In one subject 50) this condition was bilateral In another subject (case 13) the field defects were bilateral but, according to the criteria used, only e had disc drusen In the remaining seven subjects the visual field s were unilateral The affected visual fields showed slight defects itableto a lesion of the nerve-fibre bundle

cal histories

l symptoms (see also Table II)

r 12 of the 50 subjects the *presenting symptom* was ocular In four e children the strange looking optic discs were first noticed during ithalmological examination prompted by squint. In another four n the reason for the examination was external ocular discomfort ng or itching of the eyes or a sensation of soreness) Visual oms were the reason for examination in three children, in *two of* ttributable to asthenopia, in one expressed as dimness of vision ild was examined because he tilted his head when he fixed his gaze e object

f the subjects the presenting symptom was headache convulsions iting or a combination of these Three subjects were examined e of mental retardation or school difficulties and one for each of llowing reasons precocious puberty pavor nocturnus skull iality paraesthesia and *psychic alteration*

ldren had no presenting symptoms They were found to have disc during mass screening of schoolchildren or tests on siblings

f the 50 children enquiry elicited a history of eye symptoms Of ymptoms the most common were squint 5 cases and disorders of on (7 cases) Transient impairment of visual function had d *in four children*, in three of them (cases 31 35 and 44) as

recurrent unilateral dimness of vision of short duration (less than half an hour) One child (case 50) had suffered from recurrent unilateral dimness of vision for periods of longer than one hour

The commonest symptom was headache, it occured in half the subjects In four subjects the headache began at the age of 3 4 years in the others between 6 and 11 years of age Ten children had had headaches over a period of only a half to 3 5 years In twelve it was of migraine type In six children vascular headache was very frequent several attacks a week In some the headache was worst in the morning but in most it occurred in the evening and was often located in the forehead A few had visual aura and two had hemiparaesthesia. Ten patients had periodic nausea and vomiting that did not coincide with a headache although they also had headaches Vomiting was more common in the younger children and usually occurred in the morning In several children vomiting and headache occurred at about the same time thus resembling symptoms due to increased intracranial pressure A few children also had periodic abdominal pains

Convulsions were seen in twelve children these were frequent in three and infrequent in nine All twelve patients had occasional gereralized seizures which in five of them began with focal features Three children (cases 31 37 and 47) had psychomotor fits as well. In all these patients the convulsions were reduced frequency or ceased with advancing age In two cases (35 and 47) it was difficult to decide whether the seizures had been focal fits or vascular attacks Two children had vertigo

Family histories

The 50 subjects belonged to 48 families There was no consanguinity In these families migraine and unspecific headache were both common (in 30 parents 7 siblings 24 more distant relatives) Diabetes mellitus was also common, it was present in one mother and one father and a further 11 subjects had one and another 6 subjects two or more other diabetic relatives (grandparents uncles aunts and cousins are included)

Of the 87 siblings 10 had congenital anomalies and neurological symptoms (convulsions in two dyslalia in two dysphasia in one dyslexia and dysgraphia in two hydrocephalus congenital ptosis and clubfoot each in one of the siblings)

Among the 85 members of the subjects families in whom ophtalmoscopy was performed there were 12 in whom optic disc drusen were found 6 mothers 2 fathers and 4 siblings One parent with drusen (mother of cases 26 and 42) had been suspected at the age of 22 to have an intracranial malignancy because of severe headaches and papilloedema like optic discs

Clinical course

In most cases the pre and perinatal histories were uneventful Four children (cases 11, 13, 17 and 40) were born before term, but not one in the entire series was small for dates Two children (cases 5 and 38) were delivered by caesarean section and one by suction cup (case 11) In all the others delivery was normal One child was asphyctic at birth (case 40) and three children (cases 28, 37 and 47) had hyperbilirubinaemia Exchange transfusion had been done in one (case 23) In all but one (case 40) motor development was normal Eight subjects (1, 11, 14, 18, 28, 31, 37 and 38) were slow in developing language One child (case 20) had severely delayed development of speech later he had severe auditory learning difficulties and was referred to a special school for the deaf

In 46 children mental development normal Four children (cases 17, 38, 40 and 45) were mentally retarde d (IQ < 68), one of them (case 17) had congenital hypothyroidism In one boy (case 19) mental development was within normal limits during the first few years, but at the age of 7 years he suffered a psychotic disturbance

Somatic development was studied by comparing the children s heights and weights with the Finnish normal standards (Backstrom and Kantero 1971) On the day of examination all but five fell within the range of +2 standard deviations (SD) All the measurements that fell outside the range of 2 SD were above the mean One girl (case 24) aged 9 was diagnosed as having precocious puberty Another subject a boy of 14 (case 46), also had height and weight measurements 3 SD above the mean He has several very tall male relatives (over 190 cm) In three subjects, one girl (case 50) and two boys (cases 35 and 42), only the weights were above the range of 2 SD, but their heights were also above the mean The growth curves of these three subjects showed an even tendency to overweight, as is seen in »genuine» obese individuals The head circumference was studied in regard to the significance of the deviations of head circumference and height (head circumference deviation in SD minus height deviation in SD) from the means of the corresponding Finnish standards (Takkunen 1962, Backström and Kantero 1971) Of the children in whom this deviation was positive, it was greater than 1 SD in six and greater than 2 SD but less than 3 SD in one Among those in whom the difference was negative, it was greater than 1 SD in fifteen, four of them having a difference of between 2 and 3 SD

4 Findings at neuropaediatric examinations

Physical examination

Most of the children were normal in somatic appearance but ten had minor malformations flat nose bridge, hypertelorism epicanthic fold

transverse palmar crease, polydactyly and a rib anomaly Two children had small unpigmented patches of skin.

Twenty three subjects showed one or more minor neurological signs Of these the most common were motor clumsiness (18 cases) and difficulties in co-ordination (8 cases) Seven subjects had signs of upper motor neurone involvement (slight spastic hemisyndrome in two pathologically brisk tendon jerks in five) Six of these seven children had learning disabilities Muscular hypotonia was found in five children and dyslalia in four two children made slight choreiform movements with the hands

EEG findings

Most of the abnormal EEGs occured in subjects with headache Five subjects had a slightly pathological or borderline waking EEG In 22 subjects the waking EEG was pathological Four had no normal background activity Two (cases 31 and 34) aged 10 and 11 years had 3 7 Hz theta activity and one (case 45) showed 3 5 Hz delta theta activity In all other subjects the background activity was irregular and often somewhat slow

Excess of theta activity irregular (7) or in monotonous runs, and usually localized in the temporal areas (8) was noticed in 15 subjects In nine cases focal 2 3 Hz delta or 3-4 Hz delta theta waves often in short runs were seen asymmetrically in the temporal (mostly the mid temporal) or occipital regions (rather symmetrically) These features were not lateralized

An excess of fast activity 18-22 Hz was seen in the recordings of altogether six subjects (one of whom belonged to the group with slightly pathological EEGs)

Four EEGs showed focal spikes or sharp waves and five had symmetrical spike-and slow waves Four EEGs had spike-and slow wave discharges

Activation Pathological changes were noticed in 3 out of 13 *sleeping* EEGs In most cases *closing and opening of the eyes* elicited normal responses Tn three cases however closing the eyes caused occipital slow activity In four subjects a high rate of *photic stimulation* provoked generalized slow wave discharges mixed with spikes the reaction lasting 1 2 seconds. In two subjects (cases 37 and 45) voluntary *hyperventilation* elicited a generalized spike-and slow wave discharge

Radiological findings

In 44 of the 50 children in whom an X ray of the skull was taken the bony structure was considered normal. In two children there was

craniosynostosis, in one of them (case 10) the synostosis affected all sutures, and in the other (case 30) only the coronary sutures In one subject (case 2) the skull was large, suggesting hydrocephalus, but during the follow up the X ray findings were constant and no raised intracranial pressure could ever be detected In one subject (case 48) the skull was abnormally thick, with widening of the diploic space A boy aged 8 (case 16) had very broad sutures between the skull bones but no other features indicative of increased intracranial pressure Another boy aged 8 had a large broad skull with several intrasutural bones In addition, his skull radiograph showed calcification of the right plexus chorioideus This subject (case 17) was treated for congenital hypothyroidism

In three of the subjects studied calcification was demonstrable in the area of the pineal body In two subjects X ray of the left hand revealed slight decalcification of the bones These subjects had been treated with anticonvulsive drugs

Skeletal age determined from radiographs of the left hands of 38 subjects, was in 28 within the range of 1 SD on either side of the norm In five subjects skeletal age exceeded chronological age by more than 1 SD In one the difference was more than 2 SD but less than 3 SD Skeletal age was less than chronological age by more than 1 SD in five subjects in two (cases 1 and 5) of them by more than 2 but less than 3 SD

Carotid angiography was performed in nine subjects in three of them on both sides In one child (case 46) the distal branches of the left pericallosal artery were seen to be slightly dislocated downwards This was interpreted as a variant within the normal range the other angiograms revealed nothing abnormal Eight subjects of the series had been submitted to pneumoencephalography In two, there was slight ventricular enlargement according to the criteria presented by Nielsen et al (1966), in the others the encephalograms were normal

Other examinations

Three of four children considered to be mentally retarded underwent psychological testing According to the Wechsler Intelligence Scale for Children (WISC) the intelligence quotients (IQ) of those three children were between 65 and 54 corresponding to mild mental retardation

The cerebrospinal fluid examined in nine children was considered normal in all but one This child (case 30) had a slight excess of total protein and a high cell count. At follow up however the cerebrospinal fluid was normal

DISCUSSION

Frequency of the anomaly

No unselected sample of subjects comparable to that of the screening study has been examined previously in respect to the frequency of optic disc drusen In the series previously reported the subjects can be assumed to have been highly selected Furthermore because the criteria used for diagnosis of the anomaly were dissimilar detailed comparisons with the frequencies of disc drusen previously reported in clinical investigations are not valid

The frequency of disc drusen (4 in 1 076) in the sample of school children examined in I is of the same order as was found by Lorentzen (1966) whose figure of 3 4 per thousand was based on 11 subjects found to have disc drusen among 3 200 patients ecxamined on ophthalmological practice Lower frequencies have been presented by Braun (1935) who found drusen in 16 out of 15 084 patients examined at the University Eye Clinic in Greifswald and by Novokhatsky and Saldan (1972) who found an even lower prevalence 16 patients with optic disc drusen among 54 000 examined during a period of 6 years

In histopathological series however the frequencies presented are considerably higher At consecutive autopsies Tobler (1922) found disc drusen in 3 out of 370 eyes Reese (1940) found drusen in 9 discs of 893 enucleated bulbi. In a necropsy series Friedman et al. (1975) found disc drusen in 15 out of 737 cadavers in a high proportion of these eyes the drusen were minute and lay deep in the optic nerve tissue (Friedman et al. 1975) which partly explains the disparity between the clinical and histopathological studies Such drusen could not have been detected by ophthalmoscopy This explanation is probably still more true when a comparison is made between a clinical series comprising children and a histological series comprising adult subjects

Still higher frequencies have been reported in series including subjects with hereditary diseases of the retina In the population of a group of islands regarded as a genetic isolate in the Åland archipelago Forsius and Eriksson (1961) found a high frequency of tapetoretinal degeneration In addition, among the 403 inhabitants examined optic

disc drusen were certainly present in 15 and probably present in a further 19 subjects, most of them members of a family with tapetoretinal degeneration Lorentzen (1967) diagnosed optic disc drusen in 1 out of 56 patients with retinitis pigmentosa A possible explanation is that the expression of the drusen phenotype is more severe when the gene for the optic disc anomaly coincides with hereditary retinal disease

Ophthalmoscopic appearance

In the present series of 50 children with drusen of the optic disc, ophthalmoscopy showed an anomalously elevated disc associated with aberrant vascular features Superficial drusen were present in only a few of the eyes considered to have the anomaly The number of drusen per disc a maximum of 6 in the eyes in which they were seen was smaller than reported in the series of Lorentzen (1966), which consisted chiefly of adults All the cases that I found by ophthalmoscopic screening were of anomalous elevation of the disc attributable to buried drusen The rarity of superficial drusen in children accords with the evidence of the age-correlated variability of the anomaly presented by Braun (1935) and François and Verriest (1958) Although superficial drusen were more frequent in the older children of the series, no statistically significant difference at the 05 level (chi square = 1,94) in frequency could be demonstrated between those under and over the age of 11, probably because the numbers were too small The equality of the elevation of the discs regardless of the type of drusen observed could imply that the age correlated variability in the appearance of the anomaly is due to increased visibility of the concrements rather than to considerable enlargement of the total mass of drusen

The areal distribution of the superficial drusen in the series studies here was comparable to that reported by Lorentzen (1966) who saw most ot the drusen lying in the nasal quadrants of the disc In the present series, additionally an accumulation of drusen was observed in the perivascular area

Buried drusen are invisible by direct ophthalmoscopic illumination but observable when the semicircular beam of the ophthalmoscope was directed slightly to the side of the site They were also often seen adjacent to the central retinal vessels in the optic nerve tissue Furthermore, the glow produced by buried drusen in indirect illumination was often seen in small protuberances at the disc margins These protuberances, which seldom bore superficial drusen were a very common finding in the series studied Dufour et al (1971) have previously pointed out that in fluorescein angiograms the nodular appearance of the disc margins is due to buried drusen

In four fifths of the series studied the anomaly was considered bilateral. However in the subjects with bilateral disc drusen the ophthalmoscopic appearance of the discs was seldom symmetrical In the series of Lorentzen(1966) more than a quarter of the subjects had unilateral optic disc drusen This difference in bilaterality is probably due to the dissimilar criteria used for diagnosis of the anomaly

Central vascular pattern

In the series studied the central vascular pattern in the fundi with disc drusen was found to display several unusual features Vessels of aberrant origin were exceptionally frequent and even the ordinary vascular elements of the central fundus showed unusual characteristics The frequency of cilioretinal arteries was significantly higher (at the 0 01 level, chi square = 9 68) among the patients with drusen than in the control group *In his series of healthy subjects* Lorentzen (1970)found this vessel in 15 per cent of eyes In the present control series the frequency was somewhat higher In the fundi with cilioretinal arteries of the series studied the areas fed by this vessel were considered larger than in the corresponding eyes of the control series According to Dejean et al (1958) an abundant cilioretinal vascular supply in the fundi may result from a local disturbance that acted upon the central retinal vessels *during embryonic* development The extent of the cilioretinal vasculature would then be an expression of the need for replacement of that part of the retinal vasculature which because of the disturbing factor could not be supplied by vessels developing from the proximal cone of the hyaloid artery According to Hayreh (1974) retinociliary veins arising from optic discs with drusen are the result of a local circulatory disturbance produced by the pressure of the drusen. The *small tortuous veins draining outside the main venous trunk, which* were found on 4 of the 92 optic discs with drusen in the present series indicate an early tendency to form shunting opticociliary venous communications.

Quantitative analysis of the pattern of the central retinal vessels indicated that when drusen were present there was a greater tendency to early bifurcation of the vessels on and around the optic discs The measurements were made on a *series comprising fundus photographs* from 46 right eyes with optic disc drusen and compared with those of a control series comprising fundus photographs from the »better« eyes of 46 strabismic children The number of vessels was significantly higher (at the 0 01 level t = 5 81) and the summed lengths of the four main vessel branches significantly (at the 0 05 level, t = 1 97) greater in the eyes with optic disc drusen than in the controls

In addition, the quantitative analysis showed a significant (at the 0 01

level, t=4 07) preponderance of the variable used to express tortuosity in the fundi with optic disc drusen as compared with the controls This difference would be expected if vascular tortuosity is a feature associated with optic disc drusen

Hereditary disorders involving tortuosity of the retinal vessels are suggested to be manifestations of mesodermal dysplasia (Ehlers and Jensen 1973) In Down s syndrome the peripapillary retinal vessels are increased in number (Williams et al , 1973) When both tortuosity and increased numbers of vessels are found in the same hereditary ocular anomaly, as in drusen of the optic disc, an embryonic affection due to a single factor appears very likely

Fluorescein angiography revealed further features of the anomaly As compared with the fluorescein studies of the normal choroidal circulation made by Archer et al (1970), the findings in the series with optic disc drusen can be considered divergent The recurrent finding of delayed filling in the peripapillary areas of the choriocapillaris supports the suggestion that the congenital affection of the optic nerve known as optic disc drusen is associated with altered embryonic development of both the central retinal and posterior ciliary vascular systems Similar fluorescein angiographic findings have been made in nasal fundus ectasia (Hoyt, reported by Riise 1975)

The association of unusual vascular features with optic disc drusen was previously regarded as an ophthalmoscopic peculiarity (Collier 1961, Lorentzen 1966), but in recent years has attracted interest because of circulatory disturbances (Otradovec and Vladyková 1970 Karel et al 1972) Those who have had circulatory disturbances in the optic disc area may be expected to have both congenital vascular abnormalities and secondary changes in the vasculature The present series of children included few in whom the symptoms and signs could be attributed directly to circulatory disturbances in the optic nerve head Hence, most of the vascular abnormalities seen are assumed to have been present at birth No neovascularization was seen in any of the eyes studies In the few eyes in which tortuous venous vessels were seen draining outside the main venous trunk, these were presumably due to a compensatory change in the venous outflow by shunting As regards the other vascular findings of the series, a congenital aberration provides a more probable explanation than acquired vascular changes The histological studies made by Cibis (1940) on optic discs with drusen showed that both inside and outside the cells of the tiny capillaries there are deposits of a hyaline material identical with that forming the drusen Furthermore in the present series ophthalmoscopy showed that drusen accumulate in the perivascular areas of the optic discs The association of drusen with an embryonic affection of the developing vascular system would explain the

aberrant vascular features found on and around optic discs with drusen *In a small percentage* of children with disc drusen according to Henkind (1975), peripapillary subpigment epithelial haemorrahages occur in early childhood no such haemorrhages were observed in the 50 children of the present series The condition was not present in those 32 eyes examined by fluorescein angiography However, in the remaining eyes in which only ophthalmoscopy was performed peripapillary subpigment epithelial haemorrhages if very small might not have been detected

Visual function

Visual function was found to be defective in 15 subjects in 6 visual acuity was less than 1 0 and in 9 there were visual field defects In every case the subnormal visual acuity could be attributed to causes other than the drusen i e strabismus amblyopia or early age The visual field defects were slight and of the nerve-fibre bundle defect type Lorentzen (1966) considered the nerve-fibre bundle defect to be characteristic of optic disc drusen A comparison of the frequency or quantity of the defects with those of the series previously presented is not valid because in this series only the central visual field covered by the Friedmann analyzer was systematically tested

Although visual field defects were more frequent in the older children of the series no statistically significant difference at 0 05 level (chi square = 2 97) in frequency could be demonstrated between those under and over the age of 11 probably because the numbers were too small

Clinical histories

In the present series of children no uniformity of ocular symptoms was found in connection with optic disc drusen In 4 subjects visual field symptoms occurred which might be associated with the presence of drusen in the optic discs Most of the eye symptoms present in the subjects such as squint and asthenopic complaints are considered to be coincidental More than half the subjects had not had any eye symptoms

Headache was the commonest symptom in the children studied and in more than a quarter of them it was the reason or one of the reasons for the examination that led to detection of the drusen The headache was mostly of vascular type with onset between 6-11 years of age and usually occurred only for a period of some years Headache of migraine type was diagnosed in a quarter of the 50 children. The frequency of migraine in children between 7 and 15 years old has been evaluated at 2 9 7 5 % in the general population in Denmark (Dalsgaard Nielsen 1970)

In several previous series of subjects with optic disc drusen many resemblances to the present patients have been *reported* as regards the

age of onset (Lorentzen 1966, Blair and Walsh 1969) of the headaches and their frontal location (Reese 1940, Chavanne and Moreau 1952) Periodic vomiting occurred in a fifth of the children, all subjects with headache In previous reports vomiting has been a rare symptom, but it was present in one child of Reese's (1940) series

Convulsions were seen in a quarter of the children studied, most of these children also had headaches Convulsive disorders are seen quite often in subjects with optic disc drusen (Chambers and Walsh 1951, Hoyt and Pont 1962, Lorentzen 1966, Fotzsch 1970, Henkind et al 1972) The prevalence of epileptic seizures in Finnish children 14 years of age has been evaluated at 0 6 % (Amnell 1974)

School difficulties were present in more than a third of the children studied, in most of them it took the form of delay in learning to read and write Several of the children were slow to develop language, and four were later found to have dyslalia

The presence of diabetes in 2 of the 88 parents for whom detailed data were available is more than the expected frequency of 0 1 0 5 % (Maatela et al 1974) The high frequency of diabetes in the subjects' families agrees with the observations made by Collier (1961), who suggested an association between optic disc drusen and juvenile diabetes Of the subjects examined in this series, however, none was known to be diabetic In Finnish children 14 years of age the prevalence of diabetes is evaluated at 0 2 % (Amnell 1974)

Neurodevelopmental findings

The pre and perinatal histories of the subjects did not deviate from those of the average Finnish population (Hartikainen 1973) In nine subjects development of speech was delayed In four children mental retardation was present In non selected Finnish children of 14 years of age the prevalence of mental retardation is estimated at 0 92 % (Amnell 1974) Somatic development was evaluated as normal in the group studied, except for a tendency to small headedness found in more than a quarter of the children

Physical examination revealed neurological deficits in about half the children, but the signs were usually not severe In one-third of the subjects the neurological signs and developmental data in several respects resembled those found in children with minimal brain dysfunction (MBD) Only a few of the subjects were brought for examination because of symptoms attributable to MBD Therefore the frequency of children with symptoms similar to those in MBD (1/3rd) is considered high as compared with the prevalence rate of 0 29 % estimated by Amnell (1974) in Finnish children of 14 Amnell s study revealed that more than one-third of children with MBD had been born

prematurely In the present series prematurity does not explain the high frequency of symptoms similar to those seen in MBD Thus some other causal factor(s) must be responsible

Among the pathological EEGs that were recorded in about half the subjects, a characteristic finding was an irregular but otherwise normal background activity with runs of theta or delta theta activity in the mid and posterior temporal regions In addition several EEGs showed generalized activity, usually typical of the centrencephalic type of epilepsy All these findings many of which are similar to those seen in patients with migraine are in agreement with the rather sporadic cases reported in previous investigations (e g Gallais 1952 François and Vernest 1958 Pietruschka 1959 Lorentzen 1966 Rutkowska and Merz 1969 Otradovec and Vladyková 1970)

In all series most of the subjects with disc drusen had symptoms which prompted ophthalmoscopy Thus the view that drusen are accompanied by neurological disorders might have been based on false premises On the other hand, the common pleiotropism of genetic disorders would seem to support the hypothesis that a single hereditary factor has more than one manifestation.

The frequent reports of disturbances of the central nervous system in patients with optic disc drusen and the nature of the anomaly simulating phakomatosis, led Reese (1940) to speculate that there might be a connection between optic disc drusen and tuberous sclerosis In the present series no subject had retinal tumours or adenoma sebaceum. Furthermore, none showed the typical X ray findings (Parnitzke 1961) or EEG changes reported in tuberous sclerosis (della Rovera et al. 1964) Thus in the series studied, an association with tuberous sclerosis appears very unlikely

Nevertheless a surprisingly large number of neurological disorders were observed in children in whom ophthalmoscopy leading to diagnosis of drusen was performed for quite unrelated reasons In the 18 children of the present series in whom either the presenting symptom was ocular or the condition was discovered during mass screening abnormal neurological findings were so frequent and presented such a degree of conformity with the rest of the series that mere coincidence seems improbable The neurological signs and symptoms seemed to be of two subtypes which are not clear-cut. There is a group of about 15 clumsy children, most of whom had delayed speech development and later learning difficulties i.e symptoms similar to those found in minimal brain dysfunction (MBD) Another group consists of about 20 subjects with sudden convulsions and/or headache and vomiting In this group EEG changes comparable to those found in migraine were often marked, but neurological examination showed nothing abnormal.

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SUMMARY

An epidemiological study by ophthalmoscopy of 1 076 children about 7 years of age revealed four subjects with anomalous elevation of the optic disc attributable to buried drusen Superficial drusen were not seen in any of the children studied during this mass screening Neuropaediatric examination revealed neurological disorders in all the four children with the anomaly
Thus, an anomalously elevated optic disc attributable to buried drusen is not rare among children The presence of neurological symptoms and signs in the probands found by the author s ophthalmoscopic screening study indicates neurological examination of children with drusen *whether or not the cause of the blurring of the optic disc has been* difficult to assign

The ophthalmological appearance of optic disc drusen in childhood was studied in a series of 50 children comprising nearly all those under 15 years of age who were found to have disc drusen when examined in 1971—1974 at Helsinki University Eye Clinic The anomaly was associated with visual field defects in less than one-fifth of the series In more than three-quarters of the subjects it was seen as an elevated disc without superficial concrements *Although the anomaly was bilateral* in all except 8 subjects the elevation of the disc was symmetrical in less than a quarter of the series

The central vascular pattern of the eye grounds in eyes with disc drusen showed several unusual features including high frequency of a cilioretinal artery and early branching and tortuosity of the central retinal vessels The abnormality of these features was found by comparison of fundus photographs of the series studied with those of a control series comprising the »better» eyes of children treated for strabismus in the outpatient clinic. As compared with the fundi of young patients with true papilloedema the analysis showed that the fundal vascular features in papilloedema are distinguishable by the method used from those associated with optic disc drusen. In about half the angiograms of fundi with optic disc drusen, the peripapillary choroidal

Differential diagnosis

In more than half the cases of the present series, the coexistence of neurological signs and symptoms with an optic disc having the ophthalmoscopic appearance seen in true papilloedema had aroused suspicion of an intracranial process

In adults, superficial drusen afford a diagnostic key for interpretation of the benign etiology of an abnormal optic disc elevation But the drusen are seldom superficial in children For the differential diagnosis the use of a semicircular light beam of the ophthalmoscope has proved valuable This method enhances the possibilities of detecting buried drusen in the elevated disc tissue and of deciding whether oedema is present in the peripapillary retina, as in incipient papilloedema proper Examination with a slit lamp and a contact glass makes it still easier to interpret these translucent structures, but this method of biomicroscopy is not easy to apply in all child subjects

Apart from the peculiar vascular features described, the peripapillary retina was considered normal in all the optic discs with drusen of the present series In fact lack of haemorrhages has been considered characteristic of optic disc drusen in differential diagnosis (Lorentzen 1966) However, in previous reports (e g Gallais 1952 Henkind et al 1972, Karel et al 1974) papillary haemorrhages have been mentioned even in children

The vascular features of the central fundus found in eyes with disc drusen in the present series may be of some help in establishing a diagnosis Aberrant vessels and/or an unusual course or branching of the central retinal vessels are suggestive of a congenital abnormality of the disc The abundance of radial peripapillary vessels and their tortuosity are less useful in the differential diagnosis because the vascular features are similar in true papilloedema In an endeavour to check whether optic disc drusen and tortuosity are associated with supernumerary vessels and tortuosity to an indistinguishable extent, a control group of children and young adults with true papilloedema were examined by the method used for the series studied This comparison showed a significant difference of means in the number of vessels (at the level of $P > 0\ 01$, $t = 4\ 09$) similar to that seen in the comparison with strabismic children, but the difference in tortuosity, as expressed by the variable used, was less significant (at the level of $P < 0\ 05$, $t = 1\ 72$) The reason is that the supernumerary vessels associated with true papilloedema are too small to be counted by the method used In true papilloedema the displacement of the dilated veins seems not to result in as much general tortuosity of the central retinal vessels as is found in association with optic disc drusen

An epidemiological study by ophthalmoscopy of 1 076 children about 7 years of age revealed four subjects with anomalous elevation of the optic disc attributable to buried drusen Superficial drusen were not seen in *any of the children studied* during this mass screening Neuropaediatric examination revealed neurological disorders in all the four children with the anomaly

Thus an anomalously elevated optic disc attributable to buried drusen is not rare among children The *presence* of neurological symptoms and signs in the *probands found* by the author s ophthalmoscopic screening study indicates neurological examination of children with drusen whether or not the cause of the blurring of the optic disc has been *difficult to assign*

The ophthalmological appearance of optic disc *drusen in childhood* was studied in a *series of 50 children* comprising nearly all those under 15 years of age who were found to have disc drusen when examined in 1971–1974 at Helsinki University Eye Clinic The anomaly was associated with visual field defects in less than one-fifth of the series In *more than three-quarters* of the subjects it was seen as an *elevated disc* without superficial *concrements* Although the anomaly was bilateral in all except 8 subjects the elevation of the disc was symmetrical in less *than a* quarter of the series

The central vascular pattern of the *eye* grounds in eyes with disc drusen showed several unusual features including high frequency of a cilioretinal artery and early branching and *tortuosity* of the central retinal vessels The abnormality of these features was found by comparison *of fundus* photographs of the series studied with *those of a control* series comprising the »better» eyes of *children* treated for strabismus in the outpatient clinic. As compared with the fundi of young patients with *true papilloedema* the analysis showed that *the fundal vascular features* in papilloedema are distinguishable by the method used from those associated with *optic* disc drusen. In about half *the angiograms of fundi with* optic disc drusen the peripapillary choroidal

vascular pattern studied by fluorescein angiography showed delayed filling of the choriocapillaris

The symptoms, in most of the children studied, were suggestive of neurological disorders In more than half the subjects the fallacious resemblance of the anomaly to true papilloedema had contributed to suspicion of an intracranial expansive process

Neurodevelopmental evaluation in the present series showed that neurological disorders are common even in subjects brought to examination for other reasons, e g sore eyes or asthenopia The signs and symptoms showed accumulation into two subgroups One group consisted of 15 clumsy children with learning difficulties and delayed speech development The other group consisted of 20 children with sudden convulsions and/or headache and vomiting, and with EEG abnormalities but otherwise normal neurological findings In addition, there were a subgroup with miscellaneous abnormalities and a small group of children in whom no abnormalities were found apart from the eye anomaly

The study of this series of 50 children with optic disc drusen led to the following conclusion The preponderance of the buried drusen type among the optic discs of the series is explained by the age-correlated variation in the appearance of the anomaly Involvement of visual function is of little clinical importance in children with optic disc drusen

The age-correlated variation of the anomaly, some of the vascular features and the presence of neurological symptoms can be regarded as factors contributing to the great importance of the anomaly in the differential diagnosis of papilloedema in children

On the other hand, some of the vascular features found in the present study afford useful hints in the ophthalmoscopic differential diagnosis of papilloedema The presence of aberrant vessels and early branching of the central retinal vessels are characteristic of the anomaly rather than of papilloedema

The neurodevelopmental disorders found in the children studied fell into two subgroups, one similar to the symptoms of minimal brain dysfunction the other having migraine and epileptiform characteristics This observation is regarded as a challenge for further investigations

Both the vascular features of the central eye ground and the results of the neurodevelopmental evaluation in the children with optic disc drusen give reason to suppose that the hereditary anomaly of the optic nerve head known as optic disc drusen may be merely a local sign reflecting a more extended involvement developing during the embryonic period

ACKNOWLEDGEMENTS

I am deeply aware of the privilege of having been allowed to carry out this study at the Eye Clinic of Helsinki University The inspiring and encouraging interest in my work which I have experienced at our Clinic during the study has been personified by Professor Salme Vannas my teacher and chief I owe especial thanks to her for facilities at the Clinic for personal guidance in the planning and conduct of the study and for constructive criticism in preparing the manuscripts

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vascular pattern studied by fluorescein angiography showed delayed filling of the choriocapillaris

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Neurodevelopmental evaluation in the present series showed that neurological disorders are common even in subjects brought to examination for other reasons, e g sore eyes or asthenopia The signs and symptoms showed accumulation into two subgroups One group consisted of 15 clumsy children with learning difficulties and delayed speech development The other group consisted of 20 children with sudden convulsions and/or headache and vomiting, and with EEG abnormalities but otherwise normal neurological findings In addition, there were a subgroup with miscellaneous abnormalities and a small group of children in whom no abnormalities were found apart from the eye anomaly

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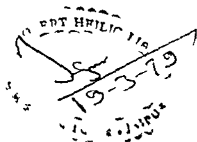
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All four showed slight to moderate pigment epithelial defects in the maculae mostly only discernible with fluorescence angiography
In all 4 cases a slight decrease of the visual acuity a mildly abnormal ERG mild concentric restriction of the field of vision and in two cases an abnormal dark adaptation curve led to the conclusion of a mild diffuse widely disseminated receptor affection of the retina (both rods and cones) The EOG appeared normal in 3 and at the lower limit of normal in 1 case On the basis of a detailed study of the literature we can conclude that the retinal lesions in chronic progressive external ophthalmoplegia may vary from benign pigmentations without functional impairment to genuine retinitis pigmentosa with all gradations of rod cone or cone rod dystrophy Emphasis is laid on the possibility of a correlation between the mitochondrial abnormalities encountered in ocular myopathy and ophthalmoplegia plus on the one hand and the retinal abnormalities on the other with special reference to a possible disorder of the utilization of pyruvate in the citric acid cycle and a loose coupling of the oxidative phosphorylation

Since 1934 when McMullen & Hine described a woman with slight pigmentations of the retina and impairment of the visual acuity in CPEO numerous papers on the combination mentioned in the title have been published. Mostly

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In all 4 cases a slight decrease of the visual acuity, a mildly abnormal ERG, mild concentric restriction of the field of vision and, in two cases, an abnormal dark adaptation curve led to the conclusion of a mild diffuse, widely disseminated receptor affection of the retina (both rods and cones). The EOG appeared normal in 3 and at the lower limit of normal in 1 case. On the basis of a detailed study of the literature we can conclude that the retinal lesions in chronic progressive external ophthalmoplegia may vary from benign pigmentations without functional impairment to genuine retinitis pigmentosa with all gradations of rod cone or cone rod dystrophy. Emphasis is laid on the possibility of a correlation between the mitochondrial abnormalities encountered in ocular myopathy and ophthalmoplegia plus on the one hand and the retinal abnormalities on the other, with special reference to a possible disorder of the utilization of pyruvate in the citric acid cycle and a loose coupling of the oxidative phosphorylation.

Since 1921 when McMullen & Hine described a woman with slight pigmentations of the retina and impairment of the visual acuity in CPEO numerous papers on the combination mentioned in the title have been published. Mostly

the nature of the pigment changes is described as *benign* implying that there is no evidence of the existence of *primary dystrophia* retinae pigmentosa or retinitis *pigmentosa*. It *is only* occasionally that the *aspect of the* fundus or perimetric electrophysiological and darkadaptation features do suggest a primary pigment *degeneration*. The benign image of the fundus *in C.P.E.O.* is highly heteromorphous as a rule *it is characterized* by diffusely disseminated or local *pigment granules* (sometimes clumps) which may or may not be associated with a fine spottiness *or a moth* eaten or pepper and salt aspect. The retinal function *as measured by* means of *psychovisual* test or eectrophysiological methods may be *slightly to moderately* impaired. As yet there is no agreement in the literature whether the condition consists of receptor damage an affection of the *pigment epithelium* or a mild manifestation of tapeto retinal degeneration after all all these theories have their advocates. The purpose of the present paper is to demonstrate *four patients with* chronic *progressive external* ophthalmoplegia and benign fundus pigmentations in whom the pigment changes exhibit characteristic *images and also* to discuss the significance of the data *obtained* by psychovisual and electrophysiological *tests*. *In the* discussion the literature of which *an extensive* study has been made will be summarized.

Methods of Investigation

The Goldmann perimeter was used for examination of the visual fields. Color vision was examined by *means of the A.O. H.R.R. test* the Nagel anomaloscope the Panel D 15 test and the 100 Hue test. The ERG was recorded with and photographed from the oscilloscope of the Henwa *retinograph* RA 35. *After 5 min preadaptation to room lighting and 10 min dark* adaptation the scotopic *ERG* was *recorded after a 2 Joule flash (flash opening 30°)* through a blue filter combined with a grey filter of different density (1.6 D, 0.6 D and 0 D). The photopic recording was carried out subsequently after 5 min *adaptation to blue light* to saturate the rods (cinemoid filter B no. 9 density background lighting 700 lux) after a 2 Joule flash of white light. The oscillatory potentials *were recorded* at the end of the scotopic registration after a 20 Joule flash (Normal values with filter 1.6 D scotopic B wave 380–400 micro V *photopic* A + B wave 150 micro V). The EOG was also recorded on the Henwa oscilloscope. For dark adaptation the Goldmann Weekers adaptometer was used. The fluorescence angiograms were made by means of the Zeiss fluorescence camera.



Fig 1
Patient 1 CPEO of 6 years standing

Case Histories

Patient 1

A man aged ? years has been suffering for 6 years from chronic progressive external ophthalmoplegia (CPEO) In his family there are several cases of ptosis In the last few years in both fundi there has been mild pigment degeneration in both maculae luteae with decrease of the visual acuity to 0.3 in the right and 0.8 in the left eye after full correction In addition there was an old scar of chorioretinitis in fundo The EEG showed extreme diffuse deceleration during hyperventilation (theta waves) The EMG of the external ocular as well as skeletal muscles indicated myopathy The muscular enzymes in the blood were repeatedly increased A biopsy from a skeletal muscle showed distinct signs of myopathy histochemical examination revealed ragged red fibers examination with the electron microscope showed mitochondrial myopathy with paracristalline inclusion bodies The results of biochemical examination were a normal Mc Ardle test a normal pyruvate lactate metabolism and only minimal indications of a loosely coupling of oxidative phosphorylation.

There was slight concentrical restriction of the peripheral visual fields Examination of the color sense and dark adaptation gave normal results Fluorescence angiography showed minimal pigmentepithelial defects in both maculae The ERG showed a slightly subnormal scotopic B wave (± 150 micro V) and a normal photopic response The EOG was normal (LP DT ratio ? 5)

Diagnosis of the retinopathy read macular degeneration with signs of mild extensive receptor damage Pigment layer function was unimpaired

Patient 2

A man aged 53 years has been suffering for the last 11 years from CPEO with in addition impaired function of the muscles of the face neck and shoulder girdle For the last few years there has been slowly progressive dysphagia There are several cases



Fig 2
Patient 2 CPLO of 11 years standing

of ptosis in his family Cineradiography revealed neither impairment of the swal lowing mechanism nor an organic steno is The first examination in 1978 had already brought to light numerous black granular pigmentations partly in reticular patrons situated peripherally in both fundi and a peripapillary chorio retinal atrophy The muscular enzymes in the blood had repeatedly shown slight increases The EMC of the ocular and skeletal muscles was myopathic The EEG indicated theta activity in the parietal portion (slowing) In addition there was mild polyneuropathy and hepato pathy after (due to?) malaria The skeletal muscle biopsy sample indicated myopathy histochemical examination revealed a few ragged red fibers which on electron micro scopical examination were found to be due to severe mitochondrial myopathy in ad dition there were numerous vacuoles and a few small angular fibers

In view of the mitochondrial myopathy including the presence of paracristalline inclusion bodies in the mitochondria the condition was diagnosed as descending ocular myopathy rather than oculo pharyngeal dystrophy also on the basis of the ophthal moplegia plus character of the condition with retinal lesions and EEG abnormalities Biochemical examination revealed a dysfunction of muscular phosphorylase (positive ischemic effort test) but no additional data that might have led to the diagnosis of Mc Ardle s disease The lactate pyruvate metabolism appeared disturbed while there was some evidence of loosely coupling of the oxidative phosphorylation

The readings of the retinal function examination were VOD = 1 0 and VOS = 0 3 (amblyopia os) after full correction There was slight concentric restriction of the visual fields Examination of color vision gave normal results and the same was true of the dark adaption The fluorescence angiogram showed slight defects and hyper pigmentations of the pigmentepithelium in the posterior poles The ERG was sco topically slightly subnormal (B wave to 180 micro V) while the photopic readings were also slightly subnormal (total A B wave difference approx 80 micro V) The EOG was entirely normal although the potential differences owing to the almost complete lack of mobility of both eyes were very low (ratio LP DT = 2 0)

The diagnosis read mild but diffuse receptor damage (both rods and cones) with intact functions of the structurally slightly changed pigment layer

Patient 3

A woman aged 51 years has been suffering for the last 22 years from CPEO complicated since many years by progressive impairment of the muscles of the face neck the girdle regions and the trunk recently dysphagia has developed The familial anamnesis is positive (slight girdle myopathy in a sister) In both fundi black reticular pigmentations could be observed in the peripheral regions identical to those seen in patient 2 The muscular enzymes in the blood were repeatedly increased, while the EMG of the ocular as well as the skeletal muscles is myopathic The EEG showed diffuse slowing Histological examination brought to light myopathic features enzyme histological studies showed ragged red fibers and electron microscopical examination revealed mitochondrial myopathy with paracristalline inclusion bodies Biochemical studies revealed a abnormal lactate pyruvate metabolism and a normal Mc. Ardles test In view of the total clinical picture and the morphological findings ophthalmoplegia plus was diagnosed

Examination of retinal function gave a visual acuity of 0 8 in the right and of 0 3 in the left eye after full correction with mild concentric restriction of the visual fields Colour vision was completely intact The ERG was slightly subnormal both scotopically and photopically (B wave to 200 micro V resp A + B wave to 80 micro V) The LOC was normal (LP DT ratio 1 8) measuring was very difficult owing to the almost completely immobile eyes Dark adaptation was slightly but distinctly impaired (1 log too high) no difference could be made between rod and cone adaptation The fluorescein angiogram showed slight depigmentations in the right macula

A diagnosis was made of mild diffuse receptor damage involving both rods and cones the pigment layer showed slight structural defects although appeared normal in function



Fig 3
Patient 3 CPEO of years standing



Fig 2
Patient 2 CPLO of 11 years standing

of ptosis in his family Cineradiography revealed neither impairment of the swallowing mechanism nor an organic stenosis The first examination in 1978 had already brought to light numerous black granular pigmentations partly in reticular patrons situated peripherally in both fundi and a peripapillary chorio retinal atrophy The muscular enzymes in the blood had repeatedly shown slight increases The EMC of the ocular and skeletal muscles was myopathic The EEC indicated theta activity in the parietal portion (slowing) In addition there was mild polyneuropathy and hepatopathy after (due to?) malaria The skeletal muscle biopsy sample indicated myopathy histochemical examination revealed a few ragged red fibers which on electron microscopical examination were found to be due to severe mitochondrial myopathy in addition there were numerous vacuoles and a few small angular fibers

In view of the mitochondrial myopathy including the presence of paracristalline inclusion bodies in the mitochondria the condition was diagnosed as descending ocular myopathy rather than oculo pharyngeal dystrophy also on the basis of the ophthalmoplegia plus character of the condition with retinal lesions and LLG abnormalities Biochemical examination revealed a dysfunction of muscular phosphorylase (positive ischemic effort test) but no additional data that might have led to the diagnosis of Mc Ardle s disease The lactate pyruvate metabolism appeared disturbed while there was some evidence of loosely coupling of the oxidative phosphorylation

The readings of the retinal function examination were VOD = 1 0 and VOS = 0 3 (amblyopia os) after full correction There was slight concentric restriction of the visual fields Examination of color vision gave normal results and the same was true of the dark adaption The fluorescence angiogram showed slight defects and hyper pigmentations of the pigmentepithelium in the posterior poles The ERG was scotopically slightly subnormal (B wave to 150 micro V) while the photopic readings were also slightly subnormal (total A B wave difference approx 50 micro V) The LOG was entirely normal although the potential differences owing to the almost complete lack of mobility of both eyes were very low (ratio LP DT 2 0)

Table I

Retinal investigations in own patients (for significance of abbreviations see Table II)

Case	Fundus		Visus		Perim	Colour	ERG	EOG	DA	FAG	Clinical context
	loc	aspect	OD	OS							
1	m c	pc	0.8	0.8	cone dim	n	slight subn	n	n	pigment defects	
2	p f	p c r t	1.0	0.5	cone dim	n	subn	n	n	pigment defects + hyperpigmentation post pole	
3	p f	p c ret	0.8	0.3	cone dim	n	subn	n	subn	pigment defects maculae	
4	p f PI	p c ret	0.3	0.5	glaucomatous	n	subn	lower limits of normal	subn	pigment defects	keratoconus glaucoma simplex



Fig 4
Patient 4 CPEO of 27 years standing

Patient 4

A man aged 47 years has been suffering since his 20th birthday from severe CPEO followed by slow progressive involvement of the muscles of the face neck shoulders and upperarms also including the laryngeal and pharyngeal muscles (monotone voice rhinolalia aperta and dysphagia) The patient was known because of keratoconus and glaucoma simplex A thymus persistens was diagnosed without immunological involvement The family anamnesis is negative In fundo black granular pigmentations could be seen in the posterior poles and more peripherally partly in linear arrangement partly as dots The muscular enzymes in the blood were repeatedly reported as moderately risen The EMG of the ocular and skeletal muscles was myopathic The EEG showed diffuse slowing A developing cardiomyopathy was suspected A skeletal muscle biopsy showed ragged red fibers which on electron microscopic examination appeared to consist of abnormal mitochondria with paracristalline inclusions bio*chemical examination of the mitochondrial function revealed some degree of loosely* coupling of oxidative phosphorylation The pyruvate lactate metabolism appeared abnormal The functional examination of the retina gave a maximum visual acuity of 0 9 for the right and 0 5 for the left eye (contactlens and/or stenopeic slit) with old glaucomatous field defects The color vision was completely normal The ERG showed subnormal scotopic responses (max B wave to 160 micro V) and photopic response as well (A + B wave to 50 micro V) The EOG was in the lower limits of normal to slight subnormal (LP/DT ratio for OD = 1 [illegible] for OS = 1 [illegible]) with the remark that the recording was extremely difficult because of the almost completely immobile eyes Dark adaptation was subjectively and objectively impaired (1 log unit too high ending) The flu rescence angiogram showed slight pigmentepithelial defect throughout the fundi

A diagnosis was made of diffuse receptor damage of both rods and [illegible] with very probable intact function of the pigmentepithelium

Table I

Retinal investigation in own patients (for significance of abbreviations see Table II)

Case	Fundus		Visus OD OS	Lens	Colour	ERG	EOG	DA	FAG	Clinical context
	Loc	aspect								
1	mac	pc	0 8 0 8	onc din	n	slight subn	n	n	pigment defects	
	pf	pc ret	1 0 0 8	c r c din	n	subn	n	n	pigment defects + hyperpigmentation post pole	
3	pf	pc ret	0 8 0 9	conc din	n	subn	n	subn	pigment defects maculae	
4	pf pi	pc ret	0 9 0 5	glaucomatous	n	subn	lower limits of normal	subn	pigment defects	keratoconus glaucoma simplex

Table II

CPFO and retinal pigment disturbances

Year	Authors	Cas	Fundus						
			loc	aspect					
1921	McMullen & Hine	2	pf mac		pc				
1941	Lelong et al	1	pf pp		pc	ret pigment			oa
1944	Barnard & Scholz	4	pf pp			ps			
1947	Walsh	29	mac	pm					
		31	pf	pm					
		241	pf		pc				
		242	pf		pc	bc		ac	oa
		243	pf pp	pm					
		244	pf pp		pc				
1948	Barré & Rohmer	1	pf		pc			ac	oa
1950	Chamlin & Billet	1	mac		pc				
		2	pf mac	pm		ps			
		3	pf pp		pc				
1952	Lord	1	pf		pc				
1955	Tuchel & Bartsch	1	pf			ret			
1956	De Ruyter	1	pf	pm					
1957	Walsh	40 = cas 29 (1947)							
		42 = cas 32 (1947)							
		266 = cas 241 (1947)							
		267 = cas 242 (1947)							
		268 = cas 243 (1947)							
		269 = cas 244 (1947)							
		270	pf mac		pc			ac	
		271	?			ps			
		274	?			bc		ac	oa
1957	Alfano & Berger	1				bc		ac	
1957	Erdbrink	1	pf mac	pm	pc			ac	
1957	Olesen	1	pf				pea		
1958	Kearns & Sayre	1	pp		pc		tr		
		2	pf pp		pc		tr	ac	
1959	Lux	1	?			ps			
1959	Doden & Baumgartner	1		(atyp degeneration)					
		2		(atyp degeneration)					

(cont.)

Table II (cont.)

Visus OD	Visus OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
6 18	6/12							suspect DRP
0								
						subj n.		
n		n						
						subj n		
		n						suspect DRP
0 30	0 0							
0 30	ODS	n						
subn		n	n					
6/10								
15 30	15 30	constr						(OD papillitis)
1/10	5 0	c scut						
15 30	1 50	n						
n	00							venathrombosis OS OD pigment abn
0	0							suspect DRP lues maculahole
	0							suspect DRI
								recorded as M Refsum but is ophthpl plus
		nstr r ng						autopsia (dystr ret p gment)
					n			
					n			

(cont)

Year	Authors	Cas	Fundus loc	Fundus aspect
1959	Thorson & Bell	1	pf	pc cs ac oa
1969	Jager et al	1	pf pp	pm
1960	Davidson	1	pf mac	ps
1960	Teasdall & Sears	2	?	pc
1960	Busti Rosner	1		
1960	Puncernau	1	mac	pc
1962	Harenko & Lappalainen	1	pf	pc
1963	Stanworth	3	pf	pc
1963	Thomas et al	1	pf mac	pc cs ac oa
1963	Chabot	1	pf pp	pc ac oa
1964	Guerci & Reny	1	pf mac	ps
1965	Fontan et al	1	pf mac	pc wp
		2	pf mac	pc
1965	Kearns	1	pf mac	pm
		(2 = cas 1 Kearns & Sayre)		
		(3 = cas 2 Kearns & Sayre)		
		4	pp	pc pea
		5		pm
		7		pm pea
		8	pf mac	pc pea
		9		pm cs
1966	Malbran	1	pf	pc ac
		2	pf mac	pm pc
1966	Daroff et al	1	pf mac	pm
1967	Zintz & Villiger	1	pf	ps
		3	ap	pm
1967	Shy et al	1	pf pp	pc ac
1968	Nagata et al	2	mac	pc?
1968	Drachman	1	pf	pc oa
		2	pf	pc
		3	pf	pc oa
1968	Rosenberg et al	1		ret pigment
		2		ret pigment

(cont.)

Visus OD OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
							autopsia no retinal abn
0 9 6 36	ringsc						
20/800							
10/10	n	n	subn		n		
0 4 0 3							
	on tr						
10 5/10	constr		exting		sc dim		suspect DRP
	constr		subn.		sc dim		
8/10	n	n	n		n		
dim	n	n	n		n		
	n		n		n		
n							
n	bl sp ↑						
n							
0 40 20 30	bl sp ↑						
20 30	bl sp ↑		subn	subn			
0 0			exting	subn	n		(VER n) suspect DRP
					subj nyctal op a		suspect DRP
			fot dim		subj n		
0 40							autopsia cone rod degeneration
n n	n	n	n		n		
1 10 1 1	c nstr	n	n		n		
6 5 6 5	c n tr						
ODS 20 5	bl p scot		sc dim				

(cont.

Year	Authors	Cas	Fundus				
			loc	aspect			
1968	Cordier et al	1	pf mac	pm			oa
1968	Brucher et al	1		tapeto ret degener			
1969	*Jellinger et al*	1	?		pc		*oa*
1969	Carton et al	1	?		pc		
1969	Whitaker & Harvey	1	pf ?		pc?		
		2	pf ?				
1969	Walsh & Hoyt	9 4	pf		pc		
1969	Stucchi et al	1	pf	pm		wp	
1969	Lessell	1	mac	pm			
1970	Ardouin et al	1	pf mac		pc	wp	
1970	Davidson	1	pf mac	pm			
		2	pf mac	pm			
1971	Castaigne et al	1	pf mac		pc	pea	
		2	pf mac	pm			
1971	Mills et al	1	pf pp		pc	pea	
		2	pf pp		pc		
1971	Alberca et al	1	pf			pea	oa
		2	pf mac	pm		pea	*oa*
1971	Simopoulos et al	1		atyp ret degeneration			
		(2 = cas 9 4 Walsh & Hoyt)					
		3		atyp ret degeneration			
		4		atyp ret degeneration			
1971	Shastri et al	1		atyp ret degeneration			
1972	Koerner & Schlote	1	pf		pc		
		2	pf		pc	wp	
		3	pf pp		pc		
		4	pf		pc	wp	
		5	pf	pm	pc		
		6	pf	pm			
1972	Koerner	1				pea	
1972	*Morriss et al*	1		ret pigment			
1972	Jean et al	1		ret pigment			
		2		ret pigment			
1972	Mukuno	2	pigment deg retina				
1972	Laplane		Same pt as cas 2 of Castaigne et al (1971)				
1972	Olson et al	(2 = cas 1 of Simopoulos et al 1971) (3 = cas 9 4 of Walsh & Hoyt 1969)					
1973	Adachi et al	1	pf	ret pigment			

(cont)

Table II (cont)

Visus OD	Visus OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
				subn.		subn.		
n	n	n				n		
n	n	n				n		
n	n			n				
5 à 6/10								
20 30	ODS							
) 10	10/10	n	n	subn.	n			
				fot. dim.				
				sc. dim.				
6 18	ODS							papilcoloboma
6 9	6 18							
		n						
10	9 10	n						
6 J	6 12							
(J	6 9	n						
d m						subj n		
		n						
		rel sc						
n	ODS	rel sc	n			n		
n	ODS	rel sc				subn		
n	ODS	n				n		
n	ODS	n	n			n		
n	ODS	rel sc				subn.		
		rel sc						
						nyctal		suspect DRP
d m	d m	c ntr		subn				

(cont.)

Table II (cont.)

Year	Authors	Cas	Fundus				
			loc	aspect			
1968	Cordier et al	1	pf mac	pm			oa
1968	Brucher et al	1		tapeto ret degener			
1969	Jellinger et al	1	?		pc		oa
1969	Carton et al	1	?		pc		
1969	Whitaker & Harvey	1	pf ?		pc?		
		2	pf ?				
1969	Walsh & Hoyt	9 4	pf		pc		
1969	Stucchi et al	1	pf	pm		wp	
1969	Lessell	1	mac	pm			
1970	Ardouin et al	1	pf mac		pc	wp	
1970	Davidson	1	pf mac	pm			
		2	pf mac	pm			
1971	Castaigne et al	1	pf mac		pc	pca	
		2	pf mac	pm			
1971	Mills et al	1	pf pp		pc	pca	
		2	pf pp		pc		
1971	Alberca et al	1	pf			pca	oa
		2	pf mac	pm		pca	oa
1971	Simopoulos et al	1		atyp ret degeneration			
		(2 = cas 9 4 Walsh & Hoyt)					
		3		atyp ret degeneration			
		4		atyp ret degeneration			
1971	Shastri et al	1		atyp ret degeneration			
1972	Koerner & Schlote	1	pf		pc		
		2	pf		pc	wp	
		3	pf pp		pc		
		4	pf		pc	wp	
		5	pf	pm	pc		
		6	pf	pm			
1972	Koerner	7				pca	
1972	Morriss et al	1		ret pigment			
1972	Jean et al	1		ret pigment			
		2		ret pigment			
1972	Mukuno	2	pigment deg retina				
1972	Laplane		Same pt as cas [illegible] of Castaigne et al (1971)				
197[illegible]	Olson et al	(2 = cas 1 of Simopoulos et al 1971)					
		(3 = cas 9 4 of Walsh & Hoyt 1969)					
1973	Adachi et al	1	pf	ret pigment			

(cont.)

Table II (cont)

Visus OD OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
	constr		subn.				DRP?
1/10 ODS			exting				typical DRP
3/10 ODS			exting		very subn		
					n	pigment epithelial atrophy	
0 60 0/ 0							
6.24 6 36	constr						
					subj nyctalopia		suspect DRP
	constr						
n n 4 10 -10		n	subn.		n		inf glaucoma
10 ODS	n		fot dim sc dim. sc d m.				
			ext ng				suspect DRP

(cont)

Table II (cont)

Year	Authors	Cas	Fundus loc	Fundus aspect
1973	Birnberger et al	1	pf pp	pc oa
1973	Tridon et al	1		ret pigment
1973	Haaz	1	pf	bc ac oa
1973	Uppal	1	pp	pc
1973	Karpati et al	1	pf	pm pc tr
1973	Mattyus et al	2	mac	pc
		3	mac	pc ac
1973	Cullen et al	1		pigment degen of ret
1973	Morgan Hughes & Mair	2		ret pigment degener
1973	Dubowitz & Brooke	1		ret pigment
		2		ret pigment
		3		ret pigment
1973	Mikol et al	1	pf pp	ps
1973	Pereda et al	1		ret pigment
1974	Pilling & Nanton	1		pc
1974	Bec & Arne	1	pf mac	pc pea
1974	Metz & Meshel	4	pf mac	pm
1974	Jancowicz et al	1		ret degeneration
		2		ret degeneration
1974	Saraux et al	4	pf	pc
1974	Zanen et al	1	*pf mac*	*pc ps pea* ac
1974	Mukuno	1		ret degeneration
		2		ret degeneration
1974	Gérard et al	1	pf	**retinite pigment*
1974	Crosby et al	1	pf	pc oa
1974	*Cotrufo et al*	1		ret pigment degener
1975	Danta et al	1	?	pc
		2	pf	pc oa
1975	Schlote & Koerner	(1 see 1972 Koerner & Schlote cas 2)		
		(2 see 1972 Koerner & Schlote cas 3)		
		3		ret degeneration
		4		
		5		"
		6		

(cont)

Table II (cont.)

Visus OD OS	Perim.	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
	constr		subn.				DRP?
1/10 ODS			exting				typical DRP
5/10 ODS			exting		very subn.		
					n	pigment epithelial atrophy	
0.60 0. 0							
[illegible]24 0.36	constr						
					subj nyctalopia		suspect DRP
	constr						
n n 4/10 10		n	subn.		n		inf glaucoma
5/10 ODS	n		fot dim. sc dim. sc dim.				
			exting				suspect DRP

(con

Year	Authors	Cas	Fundus	
			loc	*aspect*
1973	Birnberger et al	1	pf pp	pc oa
1973	Tridon et al	1		ret pigment
1973	Haaz	1	pf	bc ac oa
1973	Uppal	1	pp	pc
1973	Karpati et al	1	pf	pm pc tr
1973	Mattyus et al	2	mac	pc
		3	mac	pc ac
1973	Cullen et al	1		pigment degen of ret
1973	Morgan Hughes & Mair	2		ret pigment degener
1973	Dubowitz & Brooke	1		ret pigment
		2		ret pigment
		3		ret pigment
1973	Mikol et al	1	pf pp	ps
1973	Pereda et al	1		ret pigment
1974	Pilling & Nanton	1		pc
1974	Bec & Arne	1	pf mac	pc pea
1974	Metz & Meshel	4	pf mac	pm
1974	*Jancowicz et al*	*1*		*ret degeneration*
		2		ret degeneration
1974	Saraux et al	4	pf	pc
1974	Zanen et al	1	pf mac	pc ps pea ac
1974	Mukuno	1		ret degeneration
		2		ret degeneration
1974	Gérard et al	1	pf	rétinite pigment
1974	Crosby et al	1	pf	pc oa
1974	Cotrufo et al	1		ret pigment degener
1975	Danta et al	1	?	pc
		2	pf	pc oa
1975	Schlote & Koerner	(1 see 1972 Koerner & Schlote cas 2)		
		(2 see 1972 Koerner & Schlote cas 3)		
		3		ret degeneration
		4		
		5		
		6		

(cont)

Table II (cont)

Visus OD OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
0 9 ODS	constr					slow	Dystrophia
1/ ~ 0 0	constr		exting	un certain		filling	retinae pigmentosa typica
10/10 ODS		n	subn	n	n	pea	
6 6 ODS			n				
3/60 ODS			exting				
?/60 ODS			subn				
2 5 6 ODS			exting				
/10 ODS	constr		subn	subn	subn.		suspect DRP
	constr		nearly		strong		
	par sc		exting		subn.		
n n							
3/10 1/10							suspect DRP irisheterochromia (cataract)
0 5 ODS	bl sp ↑	abn	neg typ		subn		Diff atrophy pigment epithelium
?0/30 ODS	n	abn			subn.		
?0 0	n	n	fot dim sc dim		± n (border line) nyctal op a subj	pea	suspect DRP
	bl sp ↑	n		n	n		
	n	n			subn.		
	n	abn		abn	n		

(cont.)

Table II (cont)

Year	Authors	Cas	Fundus loc	Fundus aspect
1975	Kawasaki et al	1	pp	pc
		2		pea oa
1975	Koerner & Prebst	1	pf mac	bc ac oa
1975	Daniele et al	1	mac	ps pea
1975	Levic et al	1		cs
		2		choroideremia
		4		*myopia gravis* cs
		6		partial choroideremia cs
1975	Schmidt & Kommerell	3	*pf*	*pc*
1975	Biard	1	*pf*	*pc*
1975	Kafer	1		tapetoret degener
1975	*Santa et al*	3		ret pigment dystrophy
		5		ret pigment dystrophy
1975	Vallat et al	1	pf mac	pc bc pea ac oa
1975	Haas et al	1	?	*pc*
		2	?	pc
		3	?	pc
1975	*Lowes* (see also Reske Nielsen et al *1976*)	1	pf mac	pc cs
1976	Tamai & Holland	1	pf	pc
1976	McComish	1	pf	pc
1976	Mikol et al	(1 = same patient as 73)		
1976	Beckerman et al	1	pf	*ps*
1976	Carroll et al	1		ret degeneration
		3		ret degeneration
		4		ret degeneration
1976	Reske Nielsen et al	1		pigment retinopathy
		2		pigment retinopathy
		3		pigment retinopathy
		(4 = Lowes 1975)		

(cont)

Table II (cont)

Visus OD	Visus OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
0 9	ODS	constr		exting	un certain		slow filling	Dystrophia retinae pigmentosa typica
1/ ~ 0 05		constr						
10 10	ODS		n	subn	n	n	pea	
6 6	ODS			n				
3/60	ODS			exting				
2 60	ODS			subn				
2 5/6	ODS			exting				
7/10	ODS	constr constr par sc		subn nearly exting	subn	subn strong subn.		suspect DRP
n	n							
3/10	1/10							suspect DRP irisheterochromia (cataract)
0 5	ODS	bl sp ↑	abn	neg typ		subn		Diff atrophy pigment epithelium
90/30	ODS	n	abn			subn		
0	0	n	n	fot. dim sc dim		± n (border line) nyctal opia subj	pea	suspect DRP
		bl sp ↑ n n	n n abn	n abn		n subn n		

(co t)

Table II (cont)

Year	Authors	Cas	Fundus	
			loc	*aspect*
1976	Delobel	1	pp	pc
1976	Butler et al	1	pf pp	pc
1976	Denis et al	1		ret pigment
1976	Lou et al	(1 see Reske Nielsen cas 1)		
		(2 see Reske Nielsen cas 2)		
		(3 see ReskeNielsen cas 3)		
		4		chorioret atrophy
1977	Kamieniecka	4		ret degeneration
		6		ret degeneration
1977	Trobe & Watson	1	no abn	ac
1977	Castaigne et al	1	pp	pc pea

Abbreviations to Tables I and II CPEO and retinal pigment disturbances

cas – number of case described by author

fundus – fundus oculi

loc – localization of fundus abnormality

- pf – periphery
- pp – posterior pole
- mac – macula lutea

aspect – pm = pigment mottling fine patchy pigment disturbance pc = pigment clumps or granulae ps = pepper and salt aspect bc = bone corpuscles *cs* = *choroidal sclerosis* or atrophy pea = pigment epithelial atrophy wp = white points or flecks tr = tapetoretinal reflex ret = reticular pigmentation ac = arteriolar constriction *oa = optic atrophy*

Visus OD	Visus OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
10/10	8/10			n				
6/21				fot dim				
				sc dim				
				n				
6/15	6/15	ringsc		Bgolf dim	ubn	subn	n	
4/10	0	n		OD subn OS exting				autopsia tapeto retinal deg neration

v sus – visual acuity
perim – perimetry eventually central visual field investigation
colour – colour sense investigation
ERG – electroretinogram
EOG – electro oculogr phy
DA – dark adaptation
FAG – fluorescence angi graphy

n – normal
abn – abnormal
subn – subnormal
constr – constricted
c sc – (para) central scotoma
subj subjective
exting – extinguished
bl sp – blind spot

sc – scotopic
fot – photopic
dim – d minished
nyctal – nyctalopia
suspect DRP – suspect for pr mary dystrophia retinae pigmentosa

Table II (cont)

Year	Authors	Cas	Fundus loc	Fundus aspect
1976	Delobel	1	pp	pc
1976	Butler et al	1	pf pp	pc
1976	Denis et al	1		ret pigment
1976	Lou et al	(1 see Reske Nielsen cas 1)		
		(2 see Reske Nielsen cas 2)		
		(3 see ReskeNielsen cas 3)		
		4		chorioret atrophy
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Visus OD	OS	Perim	Colour	ERG	EOG	DA	FAG	Conclusions and clinical context
10/10 6/?1	8/10			n fot. dim sc dim n				
6/15	6/15	ringsc		Bgolf dim	subn	subn	n	
4/10	0	n		OD subn OS exting				autopsia tapeto retinal deg neration

v sus – visual acuity
perim – perimetry eventually central visual field investigation
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ERG – *electroretinogram*
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n – normal
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constr – constricted
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subj subjective
exting ext ngu shed
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sc – scotopic
fot – photopic
dim – diminished
nyctal – nyctalopia
suspect
DRP – *suspect for pr mary dystrophia* retinae pigmentosa

Discussion

In all we have found 159 cases in the literature of the combination of pigment changes *in the fundus and CPEO*. *In this group there were 108* cases with additional abnormalities of cardiac conduction and/or neurological symptoms (ophthalmoplegia plus). EEG abnormalities have been reported in as many as 47 patients in this ophthalmoplegia plus group, with a particularly high incidence of diffusely occurring theta waves; according to Whitaker & Harvey this hypersynchronous pattern disappears when the eyes are opened. EEG abnormalities may be the only neurological symptom but in the majority (30) *of the cases they were combined with ataxia, a rise of the protein level of the* CSF and occasionally other CNS symptoms. Retinal pigment changes in the CPEO without heartconduction disorders or central nervous symptoms have been reported 56 times. With only 4 exceptions, alle were cases of benign pigmentations with moderate or no functional impairment of the retina.

The combination – (CPEO and pigment changes in the fundus) – appears to exhibit no distinct hereditary pattern, not even in combination with ophthalmoplegia plus. *There was a suggestion of autosomal recessive heredity in 7* cases (4 instances of consanguinity) and of autosomal dominant heredity in 2 families (in one of these families the exceptional combination is reported of CPEO with choreoideremia, an X recessive affection, a family reported by Levic et al.), familial cases have been reported 6 times (families with more sufferers from CPEO).

It is difficult to establish at what age the retinal pigmentations occur. It is *only in the presence of severe functional impairment of the retina that the* patient will apply for ophthalmological examination before the CPEO (especially the ptosis) becomes visible (Adachi et al., Barre & Rohmer, *Mills et al.*).

As a rule, the age of onset of the CPEO can be determined adequately with the aid of photographs combined with the anamnesis. As regards the combination of ophthalmoplegia plus with pigment disorders, 85 % of the cases in *which the age at onset is recorded had their onset during the first two decades of life, divided more or less equally over the first and second decades* (45 out of 97 cases during the first and 41 during the second decade). Of the combination *of CPEO sec with retinal pigment changes 80 % had their onset during the* first 2 decades, with a tendency to increase towards the second decade (15 out of 51 cases during the first and 26 during the second decade).

The sex ratio at first sight appears to be 1:1, but after subdivision into 2 groups – ophthalmoplegia plus + pigment changes and ophthalmoplegia – sec with pigment changes – some degree of difference is discerned. In the former group the ratio amounts to practically 1:1 (m:f = 49:47), but in group 2 the ratio is 2:3 (*m*:f = 21:33). The combination of uncomplicated ophthalmoplegia with pigment changes appears to show a slight predilection for the female sex, which

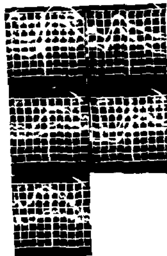


Fig 5

Composite of scotop c ERG recordings after 10 min dark adaptation with 2 Joule flash through blue filter and grey filter (1 6 density) The height of one vertical d vision in dicates 60 micron Volt Top left normal recording Top right patient 1 Mid left patient 2 Mid right patient 3 Bottom patient 4

is offset by the ophthalmoplegia plus indeed we find that the sex ratio of ophthalmoplegia plus – without retinal changes – amounts to little over 2 1 with the male sex in the lead Accordingly it is the neurological and particu larly the cardiac conduction disorders which in the combination of the so called complete Kearns syndrome (CPEO conduction disorders neurological disorders and retinal pigment changes) also determine the m f ratio of practi cally 2 1 (m f = 30 16)

As regards the retinal changes themselves many papers contain just the mention of pigment changes retinal pigment degeneration or even retinitis pigmentosa without specifying either the localization or the aspect of the pig ment changes or the results of retinal function tests From the publications in which these data are mentioned the following conclusions may be drawn

The pigment changes were determined as localized at the periphery in 78 cases and in the posterior pole in 50 cases of which 31 had a localization in the macula lutea Frequently these lesions are localized both peripherally and in the macula (40 times)

The fundus image is characterized predominantly by granular pigmentations and clumps of pigment (69 times) finely spotted deep pigmentations or a moth eaten appearance (23 times) and a pepper and salt appearance (10 times) Bone corpuscles are explicitly mentioned only 6 times Depigmentations

such as atrophy of the pigmented layer (16 times) or white spots and streaks (4 times) are described in the presence as well as in the absence of abnormal pigmentation Scherosis of the choroid is mentioned seven times and a tape to retinal reflex 3 times Constricted arterioles have been seen 16 times and papillary atrophy 20 times with the combination of the two present in 8 cases

Reticular peripheral pigmentations have been described only once (Tuchel & Bartsch) Genuine dystrophia retinae pigmentosa (retinitis pigmentosa) has been described only 3 times (Haaz Kearns & Sayre and Koerner & Probst) while 9 cases were strongly suggestive of this disease on the basis of their more or less typical fundus aspect psychovisual tests and electrophysiological readings (Cotrufo et al Käfer Kearns (case 9) Lelong et al Morriss et al Thomas et al Tridon et al Walsh 1947 (case 242) and Walsh 1957 (case 274) Four other cases are suggestive of primary retinal pigment dystrophy but the data reported are too few to allow even as much as a diagnosis of probability (Carroll et al Castaigne et al (1977) Dubowitz & Brooke Vallat et al)

There are four autopsy reports concerning the retinal condition of the affection Case 2 of Kearns & Sayre (later described again by Kearns) has been

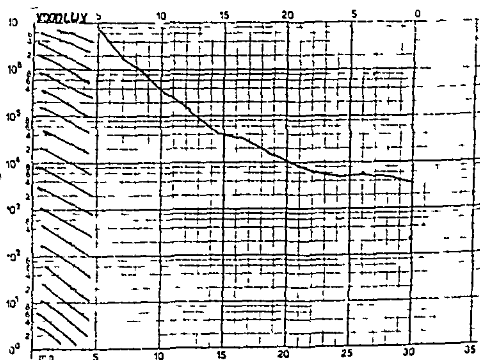


Fig 6
Darkadaptation Curve of patient 4
Dot on vertical 30 min line indicates normal end of curve

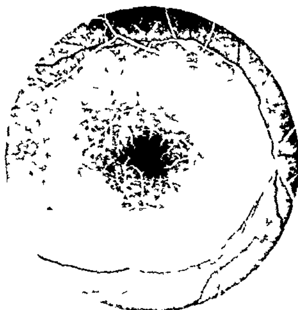


Fig ι
Fluorescence ang ogram of right macula of patient 3
Note slight central p gment epithelial defect

subjected to post *mortem* examination Examination of the eyeballs revealed local absence of receptors (rods as well as cones) with almost complete ab sence of the pigment epithelium (with only a few small scattered areas of pig ment epithelium) The external nuclear layer was also absent in spots while there was a good deal of retinal gliosis There was no distinct atrophy of the optic nerve (curiously enough it is usually found to be absent during examina tion of a retinitis pigmentosa eye with the optic microscope) while the flat pre paration of the retina revealed pseudo rosettes (these do not belong to the standard aspects of retinitis pigmentosa) Castaigne et al (19ιι) report a practically identical autopsy protocol In their patient the symptoms were localized predominantly in the posterior pole so that the clinical picture is not specific for retinitis pigmentosa (apart from the inverse type) Daroff et al in their autopsy protocol speak of a degenerations of rods and cones without further specification Jager et al find at autopsy no retinal abnormalities As Deutman mentions in general the microscopical images of dystrophia retinae pigmentosa are not entirely specific (for instance other types of tapeto retinal degeneration may show the same picture) but the clinical symptoms of Kearns patient undoubtedly indicate primary pigment degeneration of the retina The

such as atrophy of the pigmented layer (16 times) or white spots and streaks (4 times) are described in the presence as well as in the absence of abnormal pigmentation Sclerosis of the choroid is mentioned seven times and a tapeto retinal reflex 3 times Constricted arterioles have been seen 16 times and papillary atrophy 20 times with the combination of the two present in 5 cases

Reticular peripheral pigmentations have been described only once (Tuchel & Bartsch) Genuine dystrophia retinae pigmentosa (retinitis pigmentosa) has been described only 3 times (Haaz Kearns & Sayre and Koerner & Probst) while 9 cases were strongly suggestive of this disease on the basis of their more or less typical fundus aspect psychovisual tests and electrophysiological readings (Cotrufo et al Kafer Kearns (case 9) Leclong et al Morriss et al Thomas et al Tridon et al Walsh 1947 (case 242) and Walsh 1957 (case 274) Four other cases are suggestive of primary retinal pigment dystrophy but the data reported are too few to allow even as much as a diagnosis of probability (Carroll et al, Castaigne et al (1977) Dubowitz & Brooke Vallat et al)

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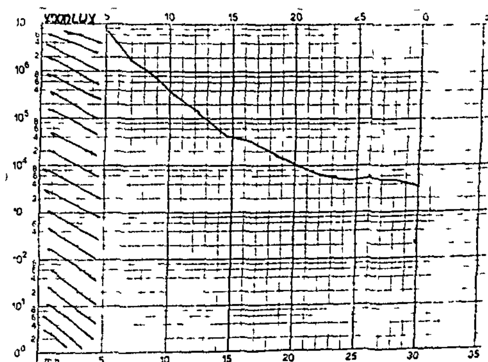


Fig 6

Darkadaptation Curve of patient 4

Dot on vertical 30 min line indicates normal end of curve

readings are reported twice and readings subnormal both photopic and scotopic are *reported* 5 times In 11 instances the ERG is reported as subnormal without further specification and 9 times it is *described* as *entirely* extinguished (this group includes the 2 patients *with choroideremia*) A normal ERG was recorded 11 times

The electro oculogram was reported 4 times as abnormal and twice as normal Failure to perform an EOG examination is explained in the majority of cases by too severe affection of ocular *movements* Examination of dark adaptation gave abnormal findings in 10 instances and subjective impairment is reported in 4 other instances (night blindness) 17 times the dark adaptation was found to be normal Trobe & Watson report subnormal *findings of* ERG EOG and dark adaptation in the presence of a normal fundus aspect Fluorescence angiography has been carried out only rarely (6 times) 4 times it revealed atrophy of the pigment layer once delayed filling and once a normal image

The pigment changes in the fundus may concern the periphery as well as the *posterior pole* the *image may* vary from a pepper and salt appearance or atrophy of the pigment epithelium to pigment clumping and bone corpuscles sclerosis of the choroid and tapeto retinal degeneration in its various forms all of which may or may not be combined with retinal vasoconstriction and papillary atrophy *Mostly the retinal affection* is of a *benign* nature but 64 cases exhibited impairment of retinal function varying from abnormal psychosensory tests to electrophysiological abnormalities abnormal darkadaptation or angiographic anomalies sometimes in combinations Even if the retinal aspect is normal the possibility of impaired function should be kept in mind *(Trobe & Watson) Opinions concerning* the *nature* of *these retinal* pigment degeneration vary from denial of the possibility of the occurrence of a primary pigment degeneration of the retina in *CPEO* to the postulate of a primary disorder in the pigment epithelium to the assumption formulated with varying degrees of vagueness of a tapeto retinal affection There is no doubt at all that genuine dystrophia retinae pigmentosa or retinitis pigmentosa may occur in CPEO it may also occur in systemic progressive muscular dystrophy various types of heredo ataxia Laurence Moon Biedl *disease etc In these diseases* also highly atypical forms of retinal pigment degeneration are possible

The uncomplicated combination of CPEO and pigment disorders of the retina practically always concerns atypical pigment changes with little or no functional impairment with *two exceptions the case* reported by Kafer and that described by Thomas et al (extinguished ERG) 2 patients with choroideremia also belong to this group In addition 24 times a (usually) mild to moderate functional impairment of the retina *has been observed* The more severe abnormalities where appearance of the fundus and impairment of retinal function *are concerned are encountered in the* combinations complicated by heartconduction disorders and/or neurological disorders Since as a rule in

other two cases mentioned (Haaz Koerner & Probst) fulfill all the clinical criteria of the same diagnosis

Remarkably numerous publications fail to report any functional examination of the ocular fundus From such values as have been mentioned however the following summary may be compiled The visual acuity is reported 20 times as normal 25 times as mildly reduced (from 0 9 to 0 5) 14 times as clearly reduced (0 4 to 0 1) 5 times as bad (0 1 to 1/60) one time only perception of finger movements was possible and in 3 instances there was even complete blindness (here the worst eye was selected as the parameter excepting the presence of other causes such as thrombosis of a venous branch amblyopia or papillitis) It would appear however that the number of patients with normal visual acuity has been larger than the 20 stated As regards the perimetric abnormalities a peripheral limitation is reported 13 times while in the central visual field an enlarged blind spot is mentioned 6 times a (relative) (para) central scotoma 8 times (in 5 of these cases only demonstrable by static perimetry) and an annular scotoma 3 times Mention of aspecific disorders of color vision are reported twice

Twenty eight times reference is made to electroretinographic abnormalities once mention is made of photopic subnormal readings scotopic subnormal



Fig 5

Fluorescence angiogram of left peripheral fundus oculi of patient 2
Note pigment granulae and clumps arranged in linear and reticular fashion

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Alberca R Coca M C Gil Peralta A Gomez Bosque P & Navarro A (1971) Miopatia ocular familiar (estudio immunoelectroforetico y de microscopia electronica) *Rev clin esp* 123 45– 2

Alfano J E & Berger J P (1957) Retinitis pigmentosa ophthalmoplegia and spastic quadriplegia. *Amer J Ophthal* 43 231– 40

Ardouin M Garnier J L Pain haud J Lefranc J & Dary J (1960) Myopathie oculaire associee a une ret nite pigm enta re atypique A propos d une observation *Rev Oto neuroophtal* 42 171–1 6

Barnard R I & Scholz R O (1944) Ophthalmoplegia and retinal degeneration *Amer J Ophthal* 27 621–624

B rre J A & Rohmer F (1948) Surdite progressive syndrome de Parinaud troubles cerebelleux dy reflexie vestibulaire croisee chez un garçon de 1? an. Troubles dégénératifs et pto is chez plusieurs membres de la famille *Confin neurol (Basel)* 8 330–335

Bec P & Arne J L (1974) L Ophtalmoplégie externe progressive et ses associations A propos d un cas avec hypertonie oculaire dégénérescence tapeto retinienne et alterations cardiaques *Arch Ophtal (Paris)* 34 8 3–856

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Biard M L (1975) L Ophthalmoplegie externe m ogenique evolutive avec anomalies ultrastructurales *Bull S c Opht l Fr* 5 515–5.2

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Birnberger K I Weindl A Struppler A Schinko I & Pongratz D (1975) Ophthal mopleg a externa progress a Eine klini che und morphologische Untersuchung *Z Neurol* 0 3 3–340

Brucher J M Dom R & Robin A (1968) Degenerescence spongieu e juvenile du système nerveux central Ses rapports avec la maladie d Hallervorden Spatz et les dystrophies neuro ax nales *Pe neu ol* 119 4 5–444

Busti Kosner L (1960) L Oftalmopleg a esterna cron ca progress va *Ann Ottal* 86 15 13?

Butl r I J & G doth N (1976) Kearns Sayre syndrome A review of a multisystem disorder of ch ld en and young adults *A ch intern Med* 136 1 90–1293

Ca ll J E Zw ll ch C W il J V & Brooke M H (19 6) Depressed ventilatory (onse n culo an son atic neuromuscular disease *Neurology (Minneap)* 26 140–14?

Cart n H C ijbels J & Brucher J M (1969) Ocular myopathy with prepubertal func t nal ca trat n synd ome *Acta neurol belg* 69 6?–?71

Ca t gne I Laplane D Esco olle R Augustin P Recondo J de Martinez Lage C J & Villanu a Eusa J V (1971) Ophthalmoplégie externe progressive avec pong ose des noyaux du tr nc cerebral *Rev neurol* 1 4 4?4–406

these cases a mitochondrial metabolic disorder is postulated which affects not only ocular and skeletal muscles but other organs as well the retinal disorder *in this condition is quite possibly also of mitochondrial origin* For that matter in the combination of CPEO (sec) and pigment changes a mitochondrial metabolic disorder is also involved but since the heart CNS etc are not affected this is less extensive and possibly less severe so that it is to be expected that the retinal disorders in these cases will also be somewhat milder This *is confirmed by data in the literature* 14 *of the* 16 cases of confirmed and suspected cases of retinitis pigmentosa fall into the first (complicated) group although the disorders of retinal function in the other patients are only mild to moderate as for instance in the group with CPEO sec and pigment changes The reported proportion of functional impairment amounts to approx 50 % in both *groups (48 of the 103 cases of the complicated and 25 of the 56 cases* of the uncomplicated group)

Conclusion

The frequently atypical aspect of the retinal lesion at the periphery as well as the posterior pole and the mildly abnormal ERG findings (photopic as well as scotopic) indicate a diffuse but mild receptor disorder involving both rods and cones In cases of this nature the EOG may be abnormal but is not necessarily so as demonstrated by our personal 3 out of 4 cases the pigment epi*thelium does not appear to be the primary site of the retinal lesion* Rather the condition appears to be a mild slowly progressive form of rod cone dystrophy (or in case of predominance of the macular lesion cone rod dystrophy) in various degrees of severity to the point of genuine retinitis pigmentosa The biochemical abnormalities attributed to *the mitochondrial disorders that have* been demonstrated in ophthalmoplegia plus may well play a causal part in the ocurrence of this retinal degeneration also loose coupling of the oxidative phosphorylation and disorders of the pyruvate lactate metabolism However so far no research in this direction has been carried out in *the various types of dystrophia retinae pigmentosa*

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Pupillomotor Spectral Sensitivity in Normals and Colour Defectives

by

Anders Hedin

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From the department of Ophthalmology
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I N T R O D U C T I O N

The sensation of colour is a cortical process Thus unlike spectral radiance colour and colour vision cannot be measured in physical terms This fact explains why it is so difficult to create an instrument capable of measuring colour vision Among the many parameters studied most depe on subjective perception e g hue discrimination saturation thresholds and absolute and in rement light thresholds x) Tests especially designed t disclose or characterize colour vision deficiencies are often based on colour confusion (pseudo-isochromatic plates and the as orting tests) or on simplified colour matching (the anomaloscope)

Objective colour vision studies are restricted to a smaller number of parameters and most often the photopic spectral ensitivity has been recorded In man electrophysiological methods like electroretinography and the recording of the visually evoked cortical potential have been used Another objective method involves the use of the pupillary reflex to light stimuli Earlier studies of the pupillomotor spe tral sensitivity have been less precise Many records are disturbed by rod intrusion Published reports on the spe tral sensitivity in colour defectives are few In most cases only a few wavelengths have been tested and the results are not conclusive

The aim of this study is to e aluate the use of the pupil reflex to *spectral stimuli for* objective colour vision te ting

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x) These and other terms used in the text are defined on p 69

L I T E R A T U R E   R E V I E W

COLOUR VISION PHYSIOLOGY

General considerations

According to the duplicity theory of vision colour vision is mediate by the retinal cones Because all colours can be matched with a mixture of three reference stimuli or primaries, normal colour vision is labelle trichromatic Trichromatism is the basis of colorimetry and does not by itself infer anything about the way different wavelengths act upon the receptors However a certain number of cone mechanisms or channels, whi react differently to stimuli of different wavelengths, must be available A minimum number of three such mechanisms is necessary But one should n conclude that only three exist although this seems reasonable from a bi economical point of view Unfortunately it is impossible at least in ma to open the retinal black box and directly record the action spectra of the cone mechanisms Instead a number of indirect approaches have been tried, resulting in a voluminous literature on the subject The proposed basic mechanisms cited in the literature have to agree with known data or colour matching spectral sensitivity, wavelength discrimination and saturation thresholds They must also fit in an acceptable model for colo vision deficiencies and thus explain abnormal colour perception (LE GRAND 1968)

YOUNG is most often cited as the originator of the trichromatic theory In 1802, he argued that a number of different retinal functions were necessary for normal colour perception, for instance three The theory was taken up by HELMHOLTZ and is today known as the YOUNG-HELMHOLTZ theory of colour vision An alternative theory based on colour psychology was put forward by HERING in 1872 he also proposed three mechanisms but defined them in a different way On the basis of the subjectively pure colours red yellow green and blue HERING postulated one red/green one yellow/ blue and one white/black channel Critical analyses of the two theories

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x) In fact an English chemist named PALMER in 1777 first presented the view that the surface of the retina is composed of particles of three different kinds corresponding to the three rays of light each of these particles is moved by its own rays (MAC ADAM 1975)

ave been presented by JUDD (1949) LE GRAND (1968) and HURVICH & JAMESON (1969)

Derivation of fundamentals from psychophysical data

Attempts to derive the spectra sensitivities of three colour mechanisms from colour mixture data of normal trichromats must fail because an endless variety of curves can be obtained depending on the choice of the primaries. The spectral sensitivity of the blue mechanism has however been obtained with the aid of a colour-matching technique (BOLLINS & MONTANABA 1973)

Accepting the assumption that dichromacy is due to the absence of one mechanism the fundamental response curves can be calculated from dichromacy data. A series of sets of fundamentals have been proposed (see JUDD 1949 1966 LE GRAND 1968) Unanimity has not been achieved mainly because of uncertainty as to the location of the convergence points of the confusion lines. Sets often referred to are those of THOMSON & WRIGHT (1953) and VOS & WALRAVEN (19 1) the latter having been modified by WALRAVEN in 1974. VOS & WALRAVEN pointed out that available data on a series of colour vision variables strongly indicates that red green dichromats lack one receptor

Other psychophysical methods are based upon binocular matching (WALTERS 194) threshold measurements in the dark after chromatic adaptation (AUERBACH & WALD 1954 1955) retinal stimulation by electrical phosphenes (MOTOKAWA 1970) and near-threshold stimuli assumed to activate only one mechanism (KRAUSKOPF & SREBRO 1965 WILSON 1969)

The blue mechanism can be eliminated by restricting the field to the central blue blind fovea (WILLMER & WRIGHT 1945) The blue mechanism can be suppressed by high frequency flicker stimuli (BRINDLEY DU CROZ & RUSHTON 1966) In this manner the red and green cone mechanisms can be isolated in red green dichromats (SPERLING 1961 SMITH & POKORNY 1975)

Chromatic adaptation is used to suppress the sensitivity of several cone mechanisms so that the remaining one can be studied in isolation. Intense chromatic adaptation was used by BRINDLEY (19 3) and WALRAVEN BOUT & LEEBEEK (1966) Studies with less intense chromatic backgrounds were first performed by STILES & CRAWFORD (1934) WALD (1964) used a yellow a purple and a blue background to isolate the responses of the blue green and red receptors respectively. There was good agreement between these curves and the difference spectra o the red and green pigments (BROWN & WALD 1963) as well as microspectrophotometry data (p 8) Similarities to STILES

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Electrophysiological studies of the cone mechanisms

Objective measurements of the cone action spectra can also be made by means of electrophysiology Three classes of cones have been identified in the carp and the turtle with the aid of measurements of photoreceptor reactions (TOMITA KANEKO MURAKAMI & PAUTLER 1967 BAYLOR & HODGKIN 1973) Corresponding primate data is not available

Chromatic adaptation has been used in electroretinographic studies for the selective suppression of cone mechanisms These studies showed three cone functions in primates with maximum sensitivity in agreement with psychophysical data (KEREN 1973 NORREN & PADMOS 1973 MEHAFFEY & BERSON 1974) Chromatic adaptation has also been used in studies of the visually evoked cortical potential and of the action spectra of the monkey s striate cortex Three functions similar to mechanisms obtained with psychophysical methods have been obtained (KELLERMANN & ADACHI-USAMI 1972 REGAN 1974 GOURAS & PADMOS 1974 ESTÉVEZ SPEKREIJSE VAN DEN BERG & CAVONIUS 1975 PADMOS & NORREN 1975)

Summarizing the subjective and objective data available on the cone mechanisms in normal trichromats it is fair to say that much evidence shows that there exist three different kinds of cones with different absorption and action spectra Each cone contains one pigment Maximum spectral reaction is at about 445 nm 535 nm and 575 nm

ZONE THEORIES AND ELECTROPHYSIOLOGICAL STUDIES OF THE VISUAL PATHWAYS

So far the discussion has been limited to the most distal part of the visual pathway i e the receptor stage In order to account for some phenomena of colour vision like simultaneous colour contrast the YOUNG-HELMHOLTZ and HERING systems have been combined to make the zone theories These theories postulate a series of stages with a trichromatic receptor stage which feeds one or several opponent-channel stages The various assumptions have been reviewed by JUDD (1949 1966) and WALRAVEN (1972) In WALRAVEN s (1966) zone model three kinds of cones feed into two opponent-colour channels and one brightness channel Blue cones contribute very little to luminous sensitivity; their number is said to be one tenth that of the red and green cones A similar model was proposed by GUTH ALEXANDER CHUMBLY GILLMAN & PATTERSON (1968) GUTH found support for his model in electrophysiological results reported by DE VALOIS (1971 1972) DE VALOIS

π-functions were also found for some pigments Chromatic adaptation has also been used in increment threshold studies (PIANTANIDA & SPERLING 1973 HARWERTH & SPERLING 1975) in critical frequency measurements (MARKS & BORNSTEIN 1973), and with flashed backgrounds (KING-SMITH & WEBB 1974)

The results of all psychophysical studies point to the existence of three cone mechanisms with maximum activity in the blue (about 440 nm) in the green (535-550 nm) and in the orange (575-585 nm) The corresponding pigments are often for simplicity called the blue, the green and the red cone pigments

Direct pigment measurements

It has not been possible to extract cone pigments from excised primate retinas The measurements of cone pigment absorption have however been done using other methods

Fundus reflectometry was introduced by RUSHTON and WEALE RUSHTON and coll (summaries in RUSHTON 1971 1972) showed that normal trichromats possess a red pigment called erythrolabe and a green pigment called chlorolabe These pigments were found to be visual pigments bleaching in accordance with predictions made on the basis of visual experiments The short wavelength pigment was not found, possibly owing to the crudeness of the method or to the supposed low blue pigment content A red and a green pigment with somewhat different spectral absorptions were also found by WEALE (1959) and RIPPS & WEALE (1963)

BROWN & WALD (1963) measured the difference spectra of excised fresh human retinas They found a green pigment with maximum absorption at about 535 nm and a red pigment with maximum absorption at about 565 nm

The question of where these pigments reside i e whether one class of cones contains one or several pigments has been clarified by microspectrophotometric measurements of single primate receptors Three classes of cones have been found with maximum absorption at 445-455 nm 525-535 nm and 555-570 nm (MARKS DOBELLE & MAC NICHOL 1964 BROWN & WALD 1964)

Direct pigment measurements thus show three kinds of cones with maximum absorption in the blue green and orange The spectral absorption registered varies somewhat but correspondence is good to psychophysical data like STILES functions the spectral sensitivity of dichromats and chromatic adaptation data

and 620 nm (Fig 7) The se sitivity in the blue region was about one log unit higher than that of the V_λ curve Humps have also been found in a number of later measurements of the AT in normals Peak wavelengths vary somewhat between studies; those at the spectral ends are at 430-450 nm and 600-620 nm

In the method of critical frequency the observer looks at a coloured field flickering with a constant frequency and adjusts the radiance until flicker is just detectable With certain flicker frequencies curves are obtained which agree with JUDD s revised V_λ curve (BORNSTEIN & MARKS 1972)

Measurement of the spectral se itivity by means of the minimum distinct border (MDB) has been described by BOYNTON and coll (BOYNTON & KAISER 1968 BOYNTON 1973) Here two juxtaposed fields of different wavelength are adjusted not to equal brightness but so that the border between them appears minimally distin t MDB luminosity is similar to that of flicker photometry and to the revised V_λ curve It has been suggested that MDB settings depend only upon the achromatic channel while in brightness matching the chromatic channels are also involved

Other methods for spectral sensitivity measurement include homochromatic contra t detection (BURKHARDT & WHITTLE 1967) magnitude-estimation (CAVONIUS & HILZ 1973) visual perceptual latency (GUTH 1964) and threshold radiance for a certain vis al acuity (BROWN PHARES & FLETCHER 1960 GRAHAM & GUTH 1970)

The nat re of the curve discontinuities has been discussed The fact that more humps than expected have been recorded especially in the blue region is of interest Because a blue peak is seen also in tritanopes and after blue adaptation ma ular pigment influence cannot be ruled out On the other hand humps are also seen in the periphery and change with chromatic adaptation No irregularities are seen in the scotopic luminosity curve which indicates that ocular media absorption is not involved Thus as proposed by STILES & CRAWFORD (1934) these humps possibly reflect the function of a trichromatic model with three underlying mechanisms

The cone mechanisms and the overall luminosity curve

GUTH DO LEY & MARROCCO (1969) and GUTH & LODGE (1973) found higher spectral sensitivities in the spectrum extremes of HBW and AT curves than in flicker photometry curves These findings can be explained by the zone model of GUTH (p 9) Only non opponent impulses contribute to visible flicker In the threshold and HBW situatio s the opponent sy tems also

recorded the spectral responses of cells in the lateral geniculate nucleus (LGN) of the macaque monkey These cells (like retinal ganglion cells GOURAS 1972) consisted of two main classes non-opponent cells which exhibited the same kind of reaction to all stimuli and colour-opponent cells with subtypes showing different reactions to red and green or to yellow and blue Using chromatic adaptation it was possible to show that red and green cones fed into the red-green opponent cells red and blue into the yellow-blue opponent cells

THE SPECTRAL SENSITIVITY OF NORMAL TRICHROMATS

The spectral sensitivity or luminosity function of the eye is the inverse of the radiance causing a certain response Because the luminosity function is fundamental for photometry, Commission Internationale de l Eclairage (CIE) in 1924 adopted a standard photopic luminosity curve V_λ A number of later studies have shown that the V_λ curve underestimates short wavelength sensitivity Thus a revised curve with higher values in the 380-470 nm range has been proposed by JUDD (WYSZECKI & STILES 1967)

Methods for spectral sensitivity measurement

In flicker photometry spectral lights are alternated with a reference light and the luminance of the spectral stimulus adjusted to minimum flicker In the step-by-step method, two juxtaposed fields of almost equal wavelength are equalized in brightness Owing to the hue similarity brightness matching in this situation is easy Spectral sensitivity curves obtained with these two methods are similar to each other and have smooth shapes In heterochromatic brightness matching (HBM) matching is made difficult by the hue differences between the reference and the test fields Irregularities in different regions of HBM curves have been shown in several studies

The spectral sensitivity can also be recorded by measuring the absolute threshold (AT) to chromatic stimuli STILES & CRAWFORD (1934) found three humps in foveal and extrafoveal AT curves (maximum at 440 nm 540 nm and 600 nm) WALD (1945) measured the AT using foveal stimuli of 10 wavelengths; his curve curve showed higher short wavelength sensitivity than the V_λ curve HSIA & GRAHAM (1952 1957) used 34 wavelengths with narrow bandwidths and presented them to the dark-adapted eyes of seven normals The individual curves and the average curve showed prominent humps peaking at 430 nm 550 nm

In the theory expounded by *KÖNIG* it is assumed that dichromats lack one of three cone mechanisms i e eith r the red mechanism (protanopes) the green (deuteranopes) or the blue (tritanopes) The FICK-LEBER fusion *hypothesis instead proposes* that two cone mechanisms or their neural pathways are fused or identical (LE GRAND 1968) *Most evidence supports* the KÖNIG *deficiency hypothesis* as will be shown below

The an malous trichromats *require three primaries for* colour matching As in dichromacy, some hues are desaturated They are classified as red-green anomalous trichromats (protanomals and deuteranomals) and yellow-blue anomalous trichromats (tritanomals) This latter type of deficiency like its dichromatic counterpart is extremely rare

Various *causes* of anomalous trichromacy have been proposed Abnormally *low (or high) pigment* con *entration was proposed by* PITT (1949) *In* HURVICH & JAMESON s model *alteration of several photopigments is a*ssumed *in both* dichromacy *and anomalous trichromacy* (HURVICH 1972 1973) Today much *evidence supports the opinion that the spectral absorption of one* pigment *is abnormal in anomalous trichromacy (see details on p 14)*

It has been known for a long time that the protan subjects (i e the *protanopes and protanomals)* have *a* reduced long wavelength *sensitivity* Deutan subjects (deuteranopes and deuteranomals) also differ from normals in luminous sensitivity but to a lesser degree Because spectral sensitivity is the main subject of this work it will be discussed in detail on p 15

In addition to the congenital colour vision deficiencies there exist acquired deficiencies which *differ from the congenital ones in a number* of ways (see e g VERRIEST 1974) Compared with the congenital deficiencies they are more often of the yellow blue type However because of their varying behaviour they have not been dealt with here This study has been limited to the congenital *red green deficiencies*

THE CONE MECHANISMS IN COLOUR VISION DEFICIENCY

According to the *KÖNIG deficiency* hypothesis the cone mechanisms *present* in dichromacy are identical with two of those operative in normal trichromacy This *hypothesis has been* supported experimentally by psychophysical *studies using the* two-colour threshold method (DE VRIES 1948) sensitivity measurements *in* the central blue blind fovea (WILLMER 1950 1955) and chromatic adaptation (WALD & BROWN 1965 WALD 1966)

contribute to luminous sensitivity especially in the more saturated ends of the spectrum Confirmatory evidence on this point has been presented by KING-SMITH (1975) and KING-SMITH & CARDEN (1976)

SPERLING and coll recorded the primate s absolute and increment threshold luminosity curves with backgrounds of different colour and luminance Overall and selective depressions were found with the backgrounds To account for the results a model was worked out in which the blue fundamental *determines* the luminous sensitivity in the short wavelength region In the *green-to-red* region the sensitivity is determined by the subtractive *linear interaction* between the weighted red and green fundamentals (SPERLING SIDLEY, DOCKENS & JOLLIFFE 1968 SPERLING & HARWERTH 1971 *HARWERTH & SPERLING 1975)*

In summary, *it can be said that cone mechanisms interact to make one* non-opponent brightness channel and two colour-opponent brightness + *chromaticity channels The relationship* between the cone fundamentals and *the overall luminosity* curve depends on the experimental conditions *In flicker and MDB* measurements, the luminosity curve can be fitted by the weighted sum of the cone sensitivity curves This cannot be done with AT *and HBM* curves These curves are broad and have humps located at about 440 nm 540 nm and 600-610 nm The location of the humps indicates that *neither the* sum nor the upper envelope of the sensitivities determine these luminosity functions These curves are probably determined by interaction between cone outputs

COLOUR VISION DEFICIENCIES

Deficient colour vision, or dyschromatopsia implies increased wavelength discrimination thresholds and increased saturation thresholds colour matching abnormalities and altered spectral sensitivity compared with normal trichromacy The two most frequent forms are dichromacy and anomalous trichromacy the rare monochromacies will not be discussed in this report The dichromats need only two primaries to match all colours; these subjects are also considered to perceive only two hues varying in saturation and lightness There are three congenital forms deuteranopia protanopia and tritanopia The former two are red-green dichromacies; the latter is the yellow-blue dichromacy Complete desaturation applies to one or two spectral colours and these wavelength bands constitute the neutral points or neutral zones

In the theory expounded by KÖNIG it is assumed that dichromats lack one of three cone mechanisms i e either the red mechanism (protanopes) the green (deuteranopes) or the blue (tritanopes) The FICK-LEBER fusion hypothesis instead proposes that two cone mechanisms or their neural pathways are fused or identical (LE GRAND 1968) Most evidence supports the KÖNIG deficiency hypothesis as will be shown below

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Various causes of anomalous trichromacy have been proposed Abnormally low (or high) pigment concentration was proposed by PITT (1949) In HURVICH & JAMESON s model alteration of several photopigments is assumed in both dichromacy and anomalous trichromacy (HURVICH 1972 1973) Today much evidence supports the opinion that the spectral absorption of one pigment is abnormal in anomalous trichromacy (see details on p 14)

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According to the KÖNIG deficiency hypothesis the cone mechanisms present in dichromacy are identical with two of those operative in normal trichromacy This hypothesis has been supported experimentally by psychophysical studies using the two-colour threshold method (DE VRIES 1948) sensitivity measurements in the central blue blind fovea (WILLMER 1950 1955) and chromatic adaptation (WALD & BROWN 1965 WALD 1966)

With *the aid of fundus* reflectometry, red-green dichromats were objectively found to have only one red-green pigment that pigment was identical with erythrolabe or chlorolabe of normal trichromats The absorption spectra agreed with the subjective spectral sensitivity of the two dichromacy classes and with psychophysical measurements of the cone mechanisms (MITCHELL & RUSHTON 1971, RUSHTON POWELL & WHITE 1973 a,b) An absence of the red *and green functions* in protanopia and deuteranopia was also shown objectively by ESTÉVEZ et al (1975) using a visually evoked cortical potential technique

The isolation of the cone mechanisms in anomalous trichromacy has been more difficult The abnormal *colour matches accepted by* anomalous *trichromats infer that their retinas contain a cone pigment* with *a* spectral absorption different from those of the normal eye An abnormal green pigment in deuteranomaly was found in two-colour threshold studies by DE VRIES (1946), in chromatic adaptation of a deuteranomalous tritanope (WALD 1966) and with intense chromatic adaptation (WALRAVEN et al 1966)

With fundus reflectometry only two pigments were found in anomalous trichromats The reason for the failure to find the third pigment could be too low pigment content or absorption similarity of the two red-green pigments RUSHTON et al (1973 c) instead used a psychophysical approach In protanomals, the normal chlorolabe and an abnormal pigment with maximum absorption at about 550 nm were found the latter pigment was called protanolabe In deuteranomals the normal erythrolabe and a corresponding abnormal pigment - *deutanolabe - with maximum absorption* at about 555 nm were recorded

A similar principle was used by PIANTANIDA BRUCH, LATCH & VARNER (1976) The absorption spectra found by this group have been used in some vertical curve shifts in the present study The spectra are shown in Fig 10 Results *in agreement* with those *cited* above were also obtained using increment *threshold measurements (PIANTANIDA & SPERLING* 1973) Maximum sensitivity of the protanomalous pigment was at about 545 nm and that of the deuteranomalous pigment at about 560 nm Calculations from anomaloscope settings have also given similar results (POKORNY SMITH & KATZ 1973) Evidence supporting the single-pigment hypothesis was recently put together by POKORNY & SMITH (1977)

In summary, the cone mechanisms of red-green dichromats have *been found* to be identical with two of those present in normal trichromats These two mechanisms are also found in anomalous trichromats Anomalous trichromats also possess a third pigment with spectral absorption close to that of the

normal red-green pigment

THE SPECTRAL SENSITIVITY OF COLOUR DEFECTIVES

Abnormalities in the spectral sensitivity of colour defectives have been shown with different methods In HM studies the average curves of protanopes and protanomals were found to be narrow and displaced towards the short wavelength region peaking at about 540 nm Average deuteranope and deuteranomalous curves differed slightly from the normal average and were displaced in the direction of longer wavelengths (PITT 1935 WRIGHT 1946) Similar results were obtained in step-by-step measurements (HECHT & SHLAER 1936)

With the AT method reduced red sensitivity in protanopia was noted by ABNEY & WATSON (1916) Sensitivity shifts in both protanopia and deuteranopia have later been found in a number of AT studies Curve maxima are at about 540 nm in protanopia and at about 570 nm in deuteranopia (HECHT & HSIA 1947 WILLMER 1950 1955 THOMSON 1951 GRAHAM & HSIA 1954 1958 HSIA & GRAHAM 1957 ZANEN WIBAIL & MEUNIER 1957 BOYNTON KANDEL & ONLEY 1959 COLLINS 1959 WALD 1966 POKORNY & SMITH 1972) Long wavelength sensitivity reduction in protanomaly has been shown by THOMSON (1951) and WALD (1966) short wavelength sensitivity reduction in deuteranomaly by COLLINS (1959)

Similar sensitivity shifts have been shown with the aid of flicker photometry; deuteranopes sensitivity is reduced for wavelengths below 50 580 nm and protanopes sensitivity is reduced for wavelengths above 550 580 nm (GRÜTZNER 1962 VERRIEST 1971 POKORNY & SMITH 1972) In the former two studies anomalous trichromats were also included No significant differences were found between them and their dichromatic counterparts Similar findings in colour defectives have also been obtained with the CFF method (BORNSTEIN & MARKS 1972)

In summary, the subjective spectral sensitivity of protans has been shown to be reduced for long wavelength stimuli The spectral sensitivity of deutans is reduced in the short wavelength region Slight or insiginificant differences exist between the dichromats and the anomalous trichromats within the protan and deutan groups

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The spectral sens tivity of the phasic pupil constriction

Early studies started already in t.e late 19th century were limited by technical diffi-ulties SACHS (1892) found equivalence between subjective luminous se sitivity and pupillomotor efficiency ABELSDORFF (1900 a) obtained in the light adapted condition a spectral sensitivity curve with maximum at about 600 nm In the dark adapted conditi-n the maximum was at about 540 nm ABELSDORFF thereby showed the Purkinje shift of the phasic pupillary response He concluded that rods or cones dominate the pupillomotor reflex depending upon the s a.e of adaptation and the stimulus intensity

S udies similar to those of SACHS & ABELSDORFF were done by BA.LER (1905) and HESS (1908 1915) SCHLE.INGER (1913 1914) found evidence that reflex activity elicited by different colours may be transmitted via more than one neuronal channel

SCHWEITZER (1956) measured the stimulus energy equivalent to a 50 per cent threshold reaction The average curve obtained with small, eccentric stimuli showed similarity to the CIE scotopic curve SCHWEITZER & BOUMAN (1958) used coloured backgrounds However their aim was not to find the spectral sensitivity of different cone mechanisms and the results were not described in detail The two curves presented show the results with a red (650 nm) background Curves peak at 20 540 nm

ALPERN & CAMPBELL (1962) measured the pupillary action spectrum using monochromatic pulses between 450 nm and 650 nm These were alternated with a white photopic stimulus or zero light Curves showing mixed scotopic and photopic contribution were recorded also when small foveal stimuli were used Only when a blue background of 100-200 td was added to foveal 2° stimuli were rods suppressed and the stray light effect eliminated The action spectrum so obtained was similar to the V_{λ} curve and was thus assumed to depend on cones only

BOUMA (1965) recorded the phasic response to coloured stimuli of eight wavelengths Curves were found to agree with the scotopic luminous sensitivity The scotopic dominance was proposed to depend upon indirect stray light stimulation of parafoveal rods But with a 450 nm conditioning field of 2 3 log scot td the foveal 1 1° spectral sensitivity curve corresponded to the photopic luminous sensitivity

KOEPPE & ALEXANDRIDIS (1968) and ALEXANDRIDIS & KOEPPE (1969) measured the phasic pupillary constriction in three normal trichromats The 11

ELECTROPHYSIOLOGICAL SPECTRAL SENSITIVITY

The spectral sensitivity can be measured by recording the electrical response from the eye or the occipital cortex (RIGGS & WOOTEN 1972) Curves obtained with standard electroretinography (ERG) are rod dominated Using different methods for rod suppression it has been possible to obtain photopic curves which agree with subjective spectral sensitivity findings Spectral sensitivity alterations in protans and deutans have been shown by DODT, COPENHAVER & GUNKEL (1958), COPENHAVER & GUNKEL (1959) DENDEN (1962) and LITH (1968)

The visually evoked cortical potential (VECP) is cone dominated Spectral sensitivity curves in agreement with psychophysical data have been recorded, using amplitude or latency criteria Reduced long wavelength sensitivity in protanopia was found by ADACHI-USAMI HECK, GAVRIYSKY & KELLERMANN (1974) In this study, a deuteranope did not differ from normals Abnormalities in the response to alternating patterns have been shown in red-green colour defectives (SMITH-KINNEY & MC KAY 1974, REGAN & SPEKREIJSE 1974)

THE SPECTRAL SENSITIVITY OF THE PUPIL CONSTRICTION

The spectral sensitivity of the steady-state pupil constriction

The relative contribution of the rods and cones to the pupil responses has long been subject to controversy LAURENS (1923) showed the Purkinje shift of the steady-state pupil response using a method with equal-energy stimuli WAGMAN & GULLBERG (1942) measured the energy necessary for a 0 5 mm pupil constriction They found the spectral sensitivity to agree with the subjective scotopic luminosity curve

BOUMA (1962) working in the photopic range, recorded a curve with a maximum at about 490 nm BOUMA later (1965) described scotopic sensitivity curves under different experimental conditions The rod dominance was deemed to depend mainly on stray light acting on rods even in situations with large responses

ALPERN & CAMPBELL (1962) registered a curve with maximum at about 530 nm The maximum of the sensitivity curve obtained by ALEXANDRIDIS & KOEPPE (1969) was at 488 nm Evidence of cone contribution was provided by DOESSCHATE & ALPERN (1965) who found a normal response at high luminance levels in a subject lacking functional rods Cone contribution was also found by ALPERN & BENSON (1953) working on directional sensitivity

The spectral sensitivity of the phasic pupil constriction

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MUNSINGER & BANKS (1974) and BANKS & MUNSINGER (1974) used the pupillary phasic response to measure the spectral sensitivity of adults and children With the aid of a neutral background, they recorded in an adult and in a 4-yr-old a spectral sensitivity curve similar to the V_λ curve With chromatic backgrounds, three cone mechanisms were found which resembled those presented by WALD (1964)

KRAATS & SLOOTER (1977) briefly described a method with alternating colour stimuli A few subjects with colour vision deficiency were studied but no results were presented Alternating colour stimulation has also been used by YOUNG & ALPERN (1977)

An infrared computer-operated pupil recording apparatus has been set up by COHEN & SAINI (1977) These authors tried to get rid of stray light rod intrusion by alternating a central $2^\circ \times 2^\circ$ field with two equal-luminance $1^\circ \times 2^\circ$ fields Rods were thought to be equally stimulated in the two conditions and cones activated to a larger degree by the central field Alternating the two fields, a response curve with a maximum at about 550 nm was recorded Good agreement with the critical frequency luminosity function was found

The pupillomotor spectral sensitivity in colour defectives

A few studies have been aimed at measuring the pupillomotor spectral sensitivity in colour defectives ENGELKING (1922) studied the steady-state pupil response He found that the pupil of protans was larger than that of normals when the eye was exposed to yellow and red light, the pupil was smaller during exposure to green and blue light No differences as compared to normals were seen in the results of the one deuteranope tested Slight deviation from the normal reaction was found in the mid-spectral region of one deuteranope studied by ADRIAN (1973) One protanope showed the expected long wavelength abnormality

GLANSHOLM HEDIN & TENGROTH (1973) recorded the steady-state pupil reactions of normals and red-green colour defectives Protans showed reduced long wavelength sensitivity and deutans showed abnormalities in both the long and short-to-medium wavelength regions

SACHS (1893) studied the phasic pupillary reaction Abnormalities were found in the response of one subject with total colour blindness and one with red-green colour blindness ABELSDORFF (1900 b) showed reduced sensitivity to red and yellow in one protanope but normal reactions in one deuteranope Similar findings were reported by HESS (1915) In ALPERN & CAMPBELL s (1962) study a protanomalous subject showed reduced pupillary sensitivity to long wavelength stimuli

A study directed at colour defectives was done by MORONE & CITRONI (1966 1967) Three equal-luminance colour stimuli were used and the response amplitudes recorded Graphs show reduced red sensitivity in one protan and reduced blue sensitivity in one deutan

Preliminary results of spectral sensitivity measurements at the cone plateau of the dark-adaptation curve were presented by HEDIN & GLANSHOLM (1975) Normals and red-green colour defectives were studied The results corresponded to those given in the present study COHEN & SAINI (1977) studied one protanope He showed reduced long wavelength sensitivity but a retained 550 nm maximum

In summary the pupillomotor spectral sensitivity curves can be said to be dominated by rod activity For measurement of the photopic sensitivity rod suppression is necessary This has been achieved using a white or blue background by recording at the cone plateau of the dark-adaptation curve and by stimulus field altenation Photopic spectral sensitivity curves in agreement with the subjective luminosity function have been obtained in normal trichromats The few studies of colour defectives have confirmed the reduced sensitivity to red in protans Findings in deutans are few and inconclusive

Because this study deals with the pupillomotor response the pupil light reflex pathways and methods for measuring the response will be reviewed in the following section

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In animals it has been shown that light stimulation initiates a change in the spontaneous parasympathetic discharge in the form of a burst of phasic impulses and an increased tonic discharge during the duration of the stimulus (SILLITTO & ZBROZYNA 1973) The efferent neurons are under the influence of a number of supranuclear pathways of cortical and brain stem origin These alter the steady-state outflow and the phasic response to light stimuli Sources of variation have been described by LOWENSTEIN & LOEWENFELD (1959 1961) LOWENSTEIN KAWABATA & LOEWENFELD (1964) and TRYON (1975) Among these are interfering sensory or psycho-sensory stimuli, spontaneous shifts in attention comfort and emotional tension In the waking state the parasympathetic outflow is inhibited With increasing tiredness the pupil constricts and the reflex amplitude changes These changes are due to reduced parasympathetic inhibition and diminished sympathetic tonus The pupil constriction may cause problems in lengthy experiments Differences in supranuclear activity and in the motor response to nerve stimuli can also account for interindividual response variability

Methods for measuring pupil size

Pupil size can be roughly measured by direct observation of the subject s pupil; precision can be increased with the use of a telescope The entoptic principle is based upon the fact that two point sources placed in front of the eye create two image discs that just touch each other if the distance between the point sources is equal to the diameter of the entrance pupil [x] The accuracy is said to be 0 05 0 2 mm The method is simple but cannot be used in darkness Other drawbacks are the visual field obstruction and the poor time resolution

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THE PUPIL

Pupil diameter variations influence the level of retinal illumination and the image forming properties of the optical system of the eye Depth of focus increases and the magnitude of spherical abberation decreases as the pupil constricts The natural pupil size has been shown to be almost optimal for visual resolution over a range of luminance levels (CAMPBELL & GREGORY 1960, WOODHOUSE 1975) The constriction following a sizeable increas in retinal illumination may be considered an aid in light adaptation WOODHOUSE & CAMPBELL (1975) proposed however that pupil constriction prepares the eye in advance for the return to dim illumination This opinion was supported by results of measurements of absolute and contrast thresholds with natural and dilated pupils

Innervation of the pupil muscles

The parasympathetic Edinger-Westphal nucleus of the oculomotor complex sends uncrossed preganglionic fibers with the third nerve to the ciliary ganglion From there postganglionic fibers reach the eye via the short ciliary nerves The sympathetic pathway originates in the diencephalon and leads over the lower cervical cord the C8-T2 roots, the upper cervical ganglion and the complex sympathetic networks to the eye (A double innervation of both iris muscles has been shown but the role of the inhibitory fibers is unsettled)

The afferent pathway for pupil light constriction follows the optic nerve In a number of studies it has been shown that the visual receptors and the receptors for pupil constriction behave identically (see e g LOEWENFELD 1966 and OHBA & ALPERN 1972) A double set of identical receptors seems improbable and we thus have reason to believe that the visual receptors act as receptors for pupil constriction

It has still not been settled whether the brain stem centers are activated by separate optic nerve fibers or by collaterals from the fibers heading for the LGV Mere economy favours the latter opinion (ALPERN et al 1974) Fibers cross in the same way as the visual fibers They then leave the visual pathway and reach the pre-tectal area From here about equal number of crossed and uncrossed neurons pass to the Edinger-Westphal nucleus Efferent neurons on both sides are equally stimulated and the consensual reflex in normals is thus equal to the direct reflex

In animals it has been shown that light stimulation initiates a change in the spontaneous parasympathetic discharge in the form of a burst of phasic impulses and an increased tonic discharge during the duration of the stimulus (SILLITO & ZBROZYNA 1973) The efferent neurons are under the influence of a number of supranuclear pathways of cortical and brain stem origin These alter the steady-state outflow and the phasic response to light stimuli Sources of variation have been described by LOWENSTEIN & LOEWENFELD (1959 1961) LOWENSTEIN KAWABATA & LOEWENFELD (1964) and TRYON (1975) Among these are interfering sensory or psycho-sensory stimuli spontaneous shifts in attention comfort and emotional tension In the waking state the parasympathetic outflow is inhibited With increasing tiredness the pupil constricts and the reflex amplitude changes These changes are due to reduced parasympathetic inhibition and diminished sympathetic tonus The pupil constriction may cause problems in lengthy experiments Differences in supranuclear activity and in the motor response to nerve stimuli can also account for interindividual response variability

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period of time can be followed by a series of pictures resolution being dependent upon picture frequency An advantage of this method is that the absolute diameter is obtained Drawbacks are the finite time resolution and the tedious measurements Electronic measuring instruments have been constructed however Accuracy is said to be 0 25 mm (PETERSEN 1956)

In the photoelectric pupillometer (MATTHES 1941) the amount of infrared radiation reflected by the eye is measured with an infrared sensitive detector Only a few per cent of incident radiation are reflected by the pupil and the total reflection thus changes with pupil area Unfortunately iris reflection differs between subjects and thus no absolute values can be obtained For calibration, the eye must also be photographed Advantages are that measurements can be performed in the dark, sensitivity is high and a continuous trace of pupil size is achieved Measuring errors can be introduced by variation of pupil position relative to the illuminated area

Infrared radiation has also been used in combination with electronic image tubes These convert the infrared image to a visible one which can be observed or photographed

More recent electronic devices are based upon optical or electronic scanning Optical scanning is performed with a flying spot of infrared radiation that passes over the sclera, iris and pupil The electronics can be set to detect which of a series of lines that has traversed the longest pupil diameter The first optical scanner was that of LOWENSTEIN & LOEWENFELD (KING 1959), the latest model was described by COHEN & SAINI (1977) Maximum error is within 1 per cent of full scale i e about 0 1 mm Time resolution depends upon the scanning frequency (generally 30-60 scans/ second) In the electronic scanning devices, the video signal from an infrared camera tube is modified so that the iris-pupil boundary is clearly identified This was the scan that passes the longest pupil diameter can be measured (ASANO FINILA SEVER STANTEN STARK & WILLIS 1962) or the number of scans which cross the pupil can be counted (GREEN & MAASEIDVAAG 1967) These systems are rather insensitive to defocussing or incidental eye movements and permit the continuous control of displacements and blinks Accuracy is about 1 per cent of full scale Time resolution depends on scanning frequency which is 30-100 scans/second

A further electronic apparatus used for pupil measurements is the image analyzer (MERTZ & ROGGENKÄMPER 1973)

MATERIAL AND METHODS

COLOUR VISION TESTING AND THE SELECTION OF SUBJECTS

Five normal trichromats and nine colour defectives served as test subjects. Their ages ranged between 25 and 45 years. A battery of colour vision tests was used to characterize their colour vision:

- The Nagel anomaloscope
- The Farnsworth Dichotomous Test Panel D-15
- The Farnsworth-Munsell 100-hue Test
- Ishihara Tests for Colour Blindness 38 plates 1970 edition
- American Optical Hardy Rand Rittler Pseudoisochromatic plates (AO H-R R) 2nd edition 1957
- Rabkin Pseudo-Isochromatic plates 2nd edition 1963
- Tokyo Medical College Color Vision Test (TMC) 1957
- Tabulae pseudoisochromaticae B K 2nd edition 1972
- The Farnsworth Tritan plate

In the anomaloscope, the observer makes a colour match between a yellow half field and a red + green half-field (see e g HEINSIUS 1973). Dichromats accept any red/green mixture; anomalous trichromats only a mixture outside the normal limits. Protans are easily separated from deutans by their reduced long wavelength sensitivity and the location of accepted matches. Matching ranges were found by the method of limits where the examiner makes a number of adjustments until all accepted ratios have been found.

The Farnsworth Panel D-15 and the Farnsworth Munsell 100 hue test are assorting tests with a number of freely moveable coloured chips (FARNSWORTH 1943). The subject is asked to arrange the chips in a continuum of hue progression and the results are plotted in diagrams. Errors in the D-15 result are evidence of significant hue confusion. Impaired hue discrimination results in characteristic error patterns in the 100-hue test. The scoring of the 100 hue results has been performed according to the proposals of KINNEAR (19) whereby one obtains easier to read diagrams with more distinct peaks.

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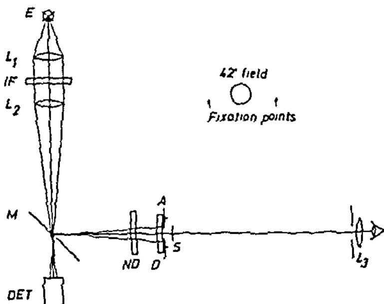


Fig 1 The optical system of the apparatus for measurement of the subjective absolute thresholds The light from the incandescent lamp E passed through the lenses L_1 and L_2 and the interference filter IF Part of the light was reflected by the mirror M through the neutral density filter ND and the diffusor D An aperture A restricted the field so that it subtended about 42' at the observation distance S was an electronic shutter opening for 50 ms The lens L_3 corrected for the finite distance to the field The detector DET measured the power transmitted through the interference filter and the mirror

Inset the test field and the two fixation lights which were separated by $2^{\circ}30$

A shutter S opening for 50 ms was placed in front of the aperture The shutter was operated by the observer when he was sure of good fixation Two faint fixation lights separated by $2^{\circ}30'$ were placed symmetrically on each side of the test field They were the cut ends of two light transmitting glass fibers At their other end there was another incandescent lamp whose o tput was adjusted until the fixation li hts were barely visible A third lens L_3 pla ed in front of the eye corrected for t e finite distance to t e observation field

The 1° foveal field was c osen in order to avoid direct rod stimulation; scot pic activity was not of main interest in this study It has been shown

The pseudo-isochromatic plates are designed for the identification of dyschromats Most series only test the red-green colour sense The yellow-blue colour sense is also tested by the tritan plate the AO H-R-R and the TMC tests A quantitative diagnosis is also given by the latter two plate series In the present study, scoring of the AO H-R-R results was done using the revised method presented by VOS VERKAIK & BOOGAARD (1972)

All tests with pigment colours were run in the illumination box designed by the author (FRISÉN & HEDIN 1973)

METHOD OF MEASURING THE SUBJECTIVE SPECTRAL SENSITIVITY

The subjective spectral sensitivity was measured as the absolute threshold This method has not been considered valid for the photopic condition, i e for measuring a different spectral characteristic than that determinant under ordinary viewing conditions (HEATH 1958 ALPERN 1968) However the results of this method are partly determined by chromatic mechanisms which were of special interest in this study The AT method was thus chosen instead of such alternatives as the flicker method, which are considered solely dependent on non-opponent activity

An apparatus was constructed to present stimuli of short duration to the fovea of the dark-adapted eye (Fig 1) The light source was an incandescent lamp fed by a stabilized variable power supply One of 16 interference filters used was interposed between the two lenses L_1 and L_2 [x)] Balzer filters with a half-height band-width of 9 nm were used, peak wavelengths were 401 421, 433 449 477 502 520 542 565, 580 591, 604 622 651 666, and 703 nm A semi-transparent mirror M reflected part of the light through a neutral density filter ND to the diffusor D The aperture A restricted the field so that it subtended 42' at the observation distance

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x) A 17th filter with peak transmission at 468 nm was also used Measurements of spectral transmission showed infrared leakage through this filter and this radiance was picked up by the detector Owing to the fact that the lamp was run on different voltages it was not possible to calculate the error introduced The results obtained with this filter have therefore been deleted

The recording apparatus

The apparatus for recording the phasic pupillary reaction consisted of infrared emitting Ga-As diodes an infrared-sensitive television camera a video tape recorder and a monitor The peak wavelength of the radiation of the four diodes was 920 nm The diodes were directed at the right eye of the subject The camera was focused on the iris plane its wavelength sensitivity reached about 950 nm It was thus possible to observe and record the pupillary reactions in darkness and no light was perceived by the subjects The continuous observation of the pupil made it possible to avoid periods of pupillary unrest

The linearity of the system was checked by measurement of circular objects within the diameter range used Deviation from linearity was maximally 1 mm on the television screen (Fig 2) Because the scale factor

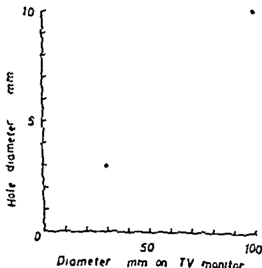


Fig 2 Linearity of the recording system measured with a series of artificial pupils placed before the television camera

was about 10 this value corresponded to about 0 1 mm of pupil diameter No attempt was made to keep the scale factor the same for all subjects The relative 10 per cent constriction created the criterion response used and the absolute diameter was not searched for (p 31)

that the central retina corresponding to a visual angle of 1° is absolutely free from rods and therefore shows a photopic spectral response even under dark adaptation (POLYAK 1941, WALD 1964, 1967)

Part of the filtered light was transmitted through the mirror and reached a detector DET [x)] This detector measured radiance power transmitted through the interference filter and the mirror The detector was checked against another power meter [xx)] After the full series of measurements, it was further calibrated by the Swedish National Testing Institution Response was uniform over the spectral range used The transmission of the ND filter was measured with the interference filters in situ The relation between radiance transmitted and radiance reflected by the mirror was measured to be constant over the spectral range used

The instrument was calibrated in radiance steps so chosen that each log unit was divided into 6 parts i e about 1 5 dB per step This step si.e was chosen after preliminary experiments with several step sizes It was a compromise between the desired precision and the necessity to perform the experiments without interfering fatigue 25 presentations of stimuli of five radiance steps were made in a predetermined sequence A typical series of yes" re-ponses (five presentations at each step) read 5 3 1 1 0 Generally all stimuli were seen at the highest and none at the lowest level Frequency-of-seeing curves were fitted by eye to the graphed results The value corresponding to 50 per cent seeing was obtained from the curves and the corresponding power calculated from the transmission data The stimulus sequence used eliminated the bias introduced in registrations in which step changes are made in an ascending or descending manner

The apparatus was not calibrated in absolute power units and the power values given in Figs 7-9 and 11-12 are relative

All measurements were done after at least 10 minutes of adaptation to total darkness This time is sufficient for cone dark-adaptation as discussed on p 32

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x) United Detector Power Meter 21 A

xx) Hewlett Packard Pyroelectric Power Meter 8334 A

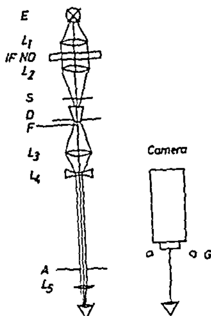


Fig 3 The optical system *for light stimulation in the pupillomotor* experiments (left) and the recording camera set up in parallel (right) The light from the incandescent lamp E passed through the lenses L_1 and L_2 and the interference and neutral filters IF ND to the diffusor D The mechanical shutter S provided stimuli of about 0 5 s duration The test field was seen through the aperture A and the lenses L_3 L_4 and L_5 Central fixation was obtained with the aid of the light guide F which was positioned in the center of the 1° field

Four infrared emitting Ga As diodes G were directed at the right eye The infrared-sensitive television camera was focused on the iris plane of this eye

The subject w s positioned using a head and chin rest Central alignment and foveal fixation was achieved with the aid of the fixation light F This was the end of a light transmitting fiber which was positioned exactly in the center of the field A separate light bulb provided orange light to the fiber; it was adjusted u til just visib e to the subject The fixation light was seen distinctly only when the eye was correctly positioned in the light beam A lens L_5 placed in front of the eye was individually chosen to enable the subject to see the fixation light without accommodation The

The stimuli were presented to the left eye (see below) The consensual reaction of the right eye was measured Owing to the equal distribution of crossed and uncrossed pupillomotor fibers, this reaction is identical with that of the stimulated eye in normal subjects (LOEWENFELD 1966, LOWENSTEIN & LOEWENFELD 1969) Because the pupillomotor spectral sensitivity of the left eye was tested, this eye was also used for colour vision testing and for measurement of the subjective spectral sensitivity

The pupil diameter was measured on the monitor to the nearest half millimeter using a caliper In order to eliminate errors introduced by lateral displacement of the camera, the vertical diameter was measured The light pulse was indicated on the sound track of the video tape The pre-stimulation diameter was the one immediately before the pulse went on Minimum diameter was obtained by stopping the tape when the pupil was seen to be at maximum constriction, the diameter was then measured one frame at a time around this tape position The pupil constriction registered was the millimeter constriction found by subtracting the minimum diameter from the pre-stimulation diameter A number of responses were measured by two scorers The difference between their figures never exceeded 0 5 mm

Time resolution was limited by the television system to 50 measurements per second This resolution was considered precise enough to allow measurement of the amplitude of responses with implicit times of 0 5-1 seconds The picture frequency corresponds to that of scanning pupillometers

Stimulation

Foveal stimulation of the left eye was achieved with an optical system set up parallel to the television camera unit (Fig 3) The light source was an incandescent lamp fed by the stabilized variable power unit Neutral and interference filters ND IF were interposed between the lenses L_1 and L_2 The anterior surface of the diffusor D constituted the test field seen through the lenses L_3 and L_4 and the aperture A The light beam entering the eye was circular in cross-section and of almost zero vergence Its diameter was 3 mm and the test field subtended 1^o at the eye Because the artificially dilated pupil was about 7 mm wide small displacements did not interfere with the passage of the entire stimulus beam into the eye Only the rod-free central retina was directly stimulated by this small-subtense stimulus

The pulse powers were calibrated in 3 dB or 4 dB steps i e the sequence was 1 10^{-8} W 5 10^{-9} W 2 10^{-9} W 1 10^{-9} W etcetera Pilot experiments showed the approximate power level necessary for a small pupil constriction Stimulation was started with a stimulus power giving about 1 mm pupil constriction and was then reduced until no response was seen on the monitor In experiments with steady adaptation pu ses were separated by about 20 seconds In experiments at the cone plateau (see below) pulses were given more frequently but not more often than every 10 seconds

Calculation of criterion power

Linear pupil constriction was plotted as a function of log stimulus power and the regression line fitting the data points calculated A criterion level of 10 percent of the average pre-stimulation diameter was chosen and the equivalent power calculated for each wavelength This value constituted the criterion power (in pW) shown in the pupillomotor diagrams

Adaptation

One experiment was done with peripheral stimulation of the dark-adapted eye The subject was first adapted to zero light for 30 minutes He was then positioned exactly in the path of the stimulus beam while fixating 18^0 to the left i e the test stimulus was dire ted at a retinal lo ation 18^0 temporal to the fixation point Ample time was alloted for readaptation between stimuli and the faint after-images disappeared long before next stimulus was given

A further experiment was performed with foveal stimulation in the dark-adapted state Test stimulation was started after 15 minutes of dark-adaptation Time lapse between wavelengths was about 2 minutes; between stimulations at least 0 seconds

One subject was tested using a blue background of about 0 1 cd/m^2 subtending about 45^0 The background was obtained with the aid of an incandescent lamp a 456 nm interference filter and four fiber optic bundles The field ce ter was a 3 mm hole for the stimulus beam The subje t adapted to the field for 5 minutes before stimulation was started

The main series of experiments was performed with the rods suppressed by repeated light adaptation; stimuli were presented at the cone plateau of the dark adaptation curve A series of calculations was made to find

pupil of the stimulated eye was dilated using two drops of 0 5 percent tropicamide

A mechanical shutter was placed between the lens L_2 and the diffusor Pulse time was 505-515 ms This stimulus duration was chosen for two reasons First up to a critical duration, there is for a certain pupil response an inverse relation between pulse time and stimulus power (ALPERN, MC CREADY & BARR 1963) Thus, a relatively long duration puts a smaller demand on pulse power The light source used was an incandescent lamp with finite output In the spectrum extremes, especially in the red and with protans, pulse power was just sufficient for a 1 mm pupil constriction The second reason for the chosen stimulus duration was the desire to eliminate bias caused by fluctuations The critical duration has been shown to be less than 500 ms (WEBSTER 1969, ALEXANDRIDIS 1971) and the small variations can thus be assumed to have no influence on the response amplitude

Chromatic stimuli of 16 wavelengths between 401 nm and 703 nm were presented with the aid of the same interference filters used in the absolute threshold studies Pulse power was measured with the radiance detector also used in the subjective measurements Calibration was performed in the following manner: The detector was placed in the position of the observer s eye Its sensitive surface exceeded that of the light beam and thus caught the total beam power The shutter was opened and the voltage of the lamp E adjusted until the detector registered the predetermined power The corresponding voltage was recorded and used in the later experiments Output powers of 10^{-9} W or more could be measured this way Pulse powers less than 10^{-9} W were obtained using an additional neutral density filter The spectral transmission of this filter was measured in situ with high incident radiance These transmission data and the output power data of each interference filter as a function of lamp voltage provided the information necessary for selection of adequate stimulus powers

The total range of stimulus powers covered more than 7 log units (see Figs 27 and 33) Pulse powers were repeatedly checked and the calibration further tested by the measurement of the 18° eccentric dark-adapted pupillomotor sensitivity As shown in Fig 16 deviation from the scotopic V'_{λ} curve was small

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the appropriate sequence of light and dark adaptation First, the absolute threshold difference between foveal cones and peripheral rods was obtained from the curves given by WALD (1945) Rod threshold was found to be maximally 3 4 log units lower than cone threshold (at about 460 nm) An elevation of rod threshold exceeding that of the cone threshold by more than this value was thus necessary

According to RUSHTON (1965 a), log rod and cone thresholds are directly proportional to the fraction of bleached photopigment

$$\log \frac{\Delta I}{A} \text{ rods} = R(1 - p)$$

and

$$\log \frac{\Delta I}{A} \text{ cones} = C(1 - p)$$

where ΔI is threshold stimulus intensity A the absolute threshold and p the fraction of non-bleached photopigment The value of the constant R is 20 (RUSHTON 1965 a), about 12 (ALPERN 1971) or 37 (RUSHTON & POWELL 1972) The constant C is 3 (RUSHTON 1965 a 1972) or 3 3 (HOLLINS & ALPERN 1973) With R = 20 and C = 3 and if $p_{cones} > 0\ 9$ and $p_{rods} < 0\ 8$ rod threshold is raised more than 3 7 log units higher than cone threshold In that situation, cones are more sensitive over the entire spectrum

Calculations were then performed using the general kinetic equation given in a series of papers by RUSHTON and ALPERN The time constant of regeneration was chosen to be 400 seconds for rods (ALPERN 1971) and 130 seconds for cones (RUSHTON 1965 b) The left eye of the subject was adapted to a circular white field subtending about 90° and with a luminance of 2000 cd/m^2 Since average pupil diameter was 7 mm the area of the entrance pupil was 38 5 mm^2 (rod bleaching) and the effective cone pupil area corrected for the STILES-CRAWFORD effect 22 3 mm^2 (LE GRAND 1968)

Calculations led to the following sequence of light and dark adaptation: The subject was first adapted to dim light for 15 minutes Then followed light adaptation (LA) dark adaptation (DA) and test stimulation -

LA 5 min DA 4 min 40 s Test 1 min

LA 1 min 20 s DA 4 min 36 s Test 1 min

LA 1 min 20 s DA 4 min 36 s Test 1 min etcetera

According to the equations used p_{cones} increased from 0 9 to 0 94 during the test minutes; p_{rods} never exceeded 0 79 Pigment bleaching and regeneration during the first test periods is illustrated in Fig 4

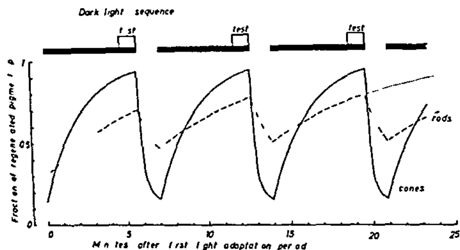


Fig 4 Bleaching and regeneration of the rod and cone pigments during the first sequences of light and dark adaptation Ordinate shows the fraction p (the amount of regenerated pigment / the total pigment content) according to the equations given in the text The dotted line shows rod pigment regeneration if dark adaptation was allowed to continue

In the upper part of the diagram are shown the periods of light adaptation dark adaptation (black bold lines) and testing

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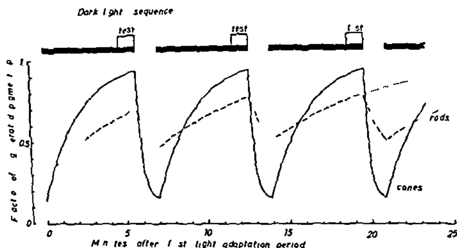


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R E S U L T S

COLOUR VISION TESTS

The normal trichromats mid-matching points on the Nagel anomaloscope were between 40 and 42 The average value of a large number of normal subjects was 41 with this instrument The matching ranges were 0-2 scale units One subject failed one pseudo-isochromatic plate in three tests, another one plate only These errors were within the accepted limits for normal trichromats The other three subjects read all plates correctly All performed normally on the D-15 test One subject s error score on the 100-hue test was high (86) This value was within the limits given by VERRIEST VANDEVYVERE & VANDERDONCK (1962) for his age group His error pattern was anarchic indicating an overall reduction in wavelength discrimination (Fig 5)

The colour defectives were classified according to their performance on the anomaloscope The anomalous trichromats accepted only mixtures in the protanomalous or deuteranomalous ranges protanomals anomaly quotients were 0 13 and 0 2 and deuteranomals 2 8 and 5 5 The matching ranges of the anomalous trichromats were 1-5 scale units The extreme deuteranomalous subject accepted mixtures in the entire green range Dichromats accepted all red-to-green mixtures

All defectives missed the blue square on the tritan plate They also failed the Ishihara the AO H-R-R the B -K the Dvorine and the TMC tests In two cases the qualitative classification given by the Ishihara test was incorrect In two cases no classification was possible with the AO H-R-R and Dvorine plates In three cases the TMC plates did not enable classification The degree of deficiency according to the AO H-R-R and the TMC plates did not correspond to the anomaloscope classification It is known however that these tests fail to give a correct classification in a certain number of cases (FREY 1963 LAKOWSKI 1969)

Two anomalous trichromats performed normally on the D-15 test The other colour defectives failed the test and were correctly type-identified This test is not designed to pick up slight deficiencies (FARNSWORTH 1943 LINKSZ 1966)

The 100 hue result of one protanomalous subject was normal (error score 28) The error scores of the other eight colour defectives all exceeded the 95 percent limit given by VERRIEST et al (1962) The dominant error axis corresponded to the anomaloscope result except in one protanomalous subject who laid the test chips in a deutan pattern (Fig 6)

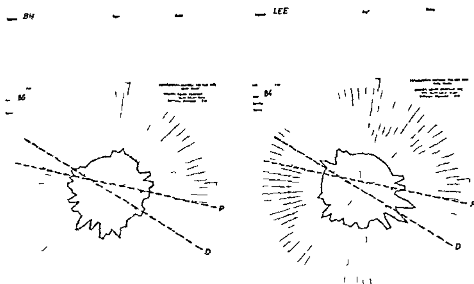


Fig 5 (left) The Farnsworth-Munsell 100 hue error pattern of a normal trichromat who e error score was 86 Included are the lines of maximum error characteristic of protan (P) and deutan (D) defects

Fig 6 (right) The Farnsworth Munsell 100-hue error pattern of one protanomalous subject

The re ults of the tests determined without doubt the colour vision dia os s of each subject In some cases one pigment test gave results which were not in agreement with the anomaloscope In these cases the e ults of all other tests were in agreement however A. to the spectral sensitivity within each deficiency group too much emphasis hould not be put upon the performance on the pigment tests considering the lack of correspondence shown by VERRIEST (1971)

SUBJECTIVE SPECTRAL SENSITIVITY

The individual absolute threshold curves of the five normal trichromats are graphed together with the pupillomotor spectral sensitivity curves in Figs 19-23 The average curve is presented in Figs 7 and 24, in Fig 24 also with its S D The relative threshold power values are given in the subjective results

Some of the dips and humps of the individual curves are smoothed out in the average curve However, the short wavelength peak at about 430 nm is still visible There are also irregularities in the wavelength region of 560-620 nm

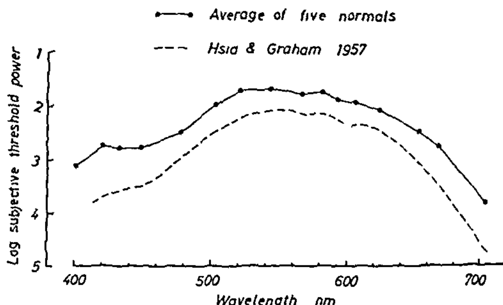


Fig 7 The average subjective spectral sensitivity of the five normal trichromats Ordinate is log threshold power as recorded with the apparatus shown in Fig 1 The average normal trichromat curve of HSIA & GRAHAM (1957) has been included It has arbitrarily been adjusted in height for best comparison

The subjective spectral sensitivity of the two protanopes is given in Fig 8 Here the points have been shifted vertically so that the thresholds are put equal for 401 nm 401 nm is the wavelength of assumed least sensitivity difference between normals and protanopes these colour defective are considered to lack the long wavelength cone pigment

The data of the two protanopes shows reduced sensitivity from about 500 nm to the red end of the spectrum

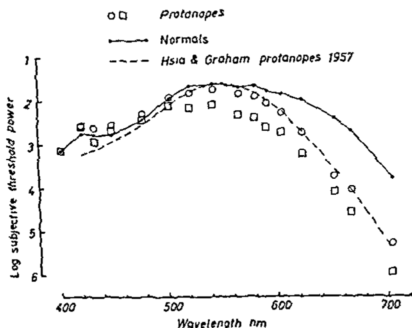


Fig 8 The subjective spectral sensitivity of the two protanopes The data points have been vertically adjusted to equality with the average normal curve at 401 nm (see text) The average protanope curve of HSIA & GRAHAM (1957) has been vertically shifted to the same maximum as the curve of the normal trichromats

The points of the two deuteranopes have likewise been vertically sifted (Fig 9) Here equalization has been made at 703 nm Deuteranopes red receptor is considered identical with that of normals Only one receptor operates in the far red and thus solely determines the spectral sensitivity A finding supporting the adjustments made is GRAHAM & HSIA s (1958) demonstration of equal threshold energies in normals and deuteranopes in the red beyond 640 nm

No sensitivity reduction is seen in the two deuteranope curves on the contrary they exhibit increased sensitivity over the whole spectrum range

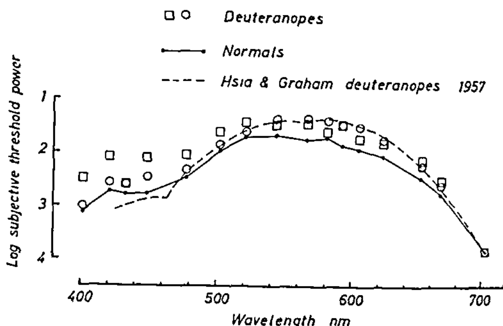


Fig 9 The subjective spectral sensitivity of the two deuteranopes The data points have been vertically shifted to equality with the average normal curve at 703 nm (see text) The average curve of the deuteranopes of HSIA & GRAHAM (1957) has been adjusted vertically in the same way

Vertical adjustment of the curves of the <u>anomalous trichromats</u> has also been done As discussed on p 14 much evidence supports the theory that anomalous trichromats have an abnormal pigment whose spectral absorption is shifted in the direction of the other normal red-green pigment Overall spectral sensitivity is assumed to be least altered at the point where the spectral absorption of the normal (missing) and abnormal pigment is identical This principle is illustrated in Fig 10 in which the spectral sensitivity curves of PIANTANIDA et al (1976) are presented For protanomals the test wavelength nearest the crossing point is 565 nm and for deuteranomals 542 nm (arrows) To be valid this adjustment requires that the overall spectral sensitivity curve is made up of the sum of the cone action spectra It further demands small pigment density variation It is not possible to prove that any of these requirements have been met but the procedure used is considered to be the best available

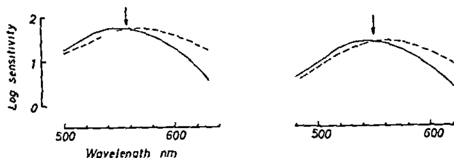


Fig 10 The spectral sensitivities of the normal red and green pigments and the abnormal protanomalous and deuteranomalous pigments (from PIANTANIDA et al 1976) The curves have been drawn to the same maximum Arrows indicate the wavelengths with assumed minimum spectral sensitivity difference between normals and anomalous trichromats In protanomaly (left) the nearest te t wavelength was 565 nm in deuteranomaly (right) 542 nm

The extreme deuteranomalous subject has been treated like the other deuteranomalous subjects although his abnormal pigment may be even closer to the red pigment considering his poor wavelength di crimination his error score on the 100 hue test was 209

The sensitivity o the two protanomalous subjects (Fig 11) was reduced for wavelengths over 565 nm

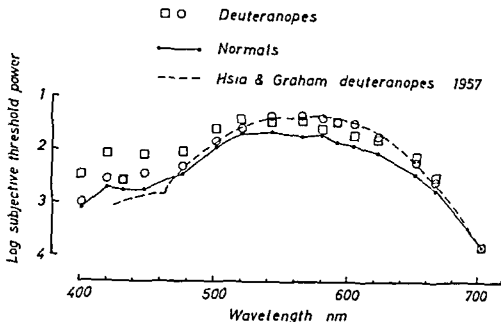


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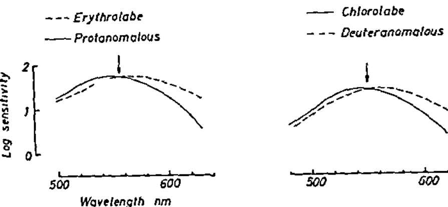


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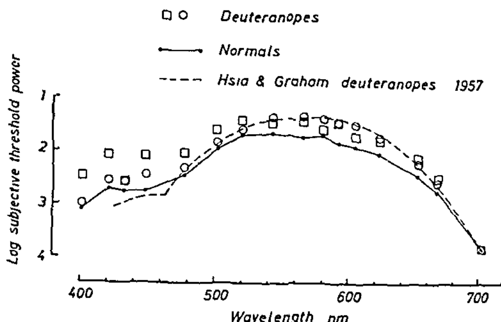


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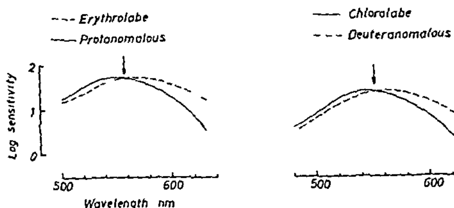


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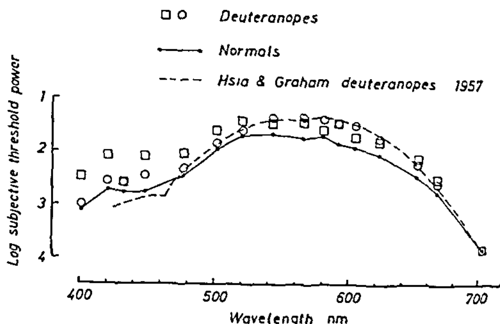


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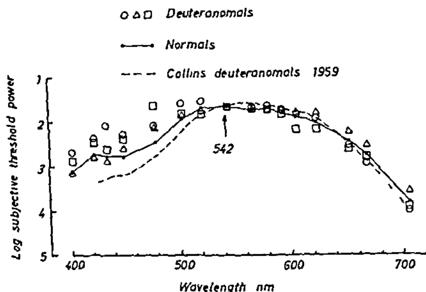


Fig 12 The subjective spectral sensitivity of the three deuteranomalous subjects The data points and the average curve of deuteranomals given by COLLINS (1959) have been vertically shifted to equality with the average curve of the normal trichromats at 542 nm (see text and Fig 10)

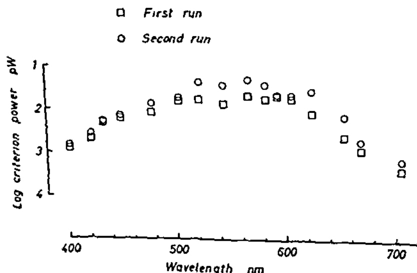


Fig 13 Test and retest of the pupillomotor spe tral sensitivity of a normal trichromat Ordinate is the log criterion power in pW

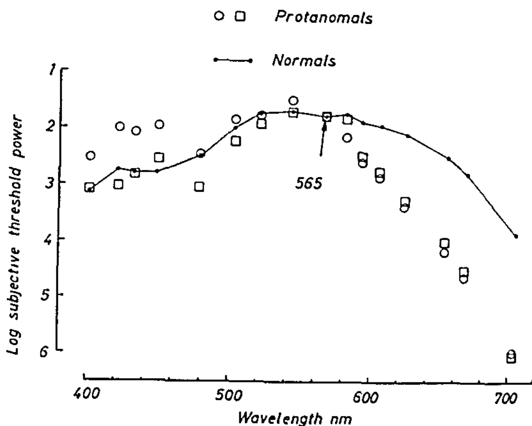


Fig 11 The subjective spectral sensitivity of the two protanomalous subjects The data points have been vertically shifted to equality with the average normal curve at 565 nm (see text and Fig 10)

Only minor discrepancies from the average normal curve were found in the deuteranomalous subjects except for some sensitivity increase in the short wavelength region (Fig 12)

sensitivity obtained depends upon the criterion chosen if the slope of the regression lines varies between wavelengths It is evident from Fig 15 that the slopes did vary but no systematic wavelength dependence is seen The individual data points of the other subjects have not been graphed Point spread and slope variation in the other subjects were similar to those depicted in Fig 1

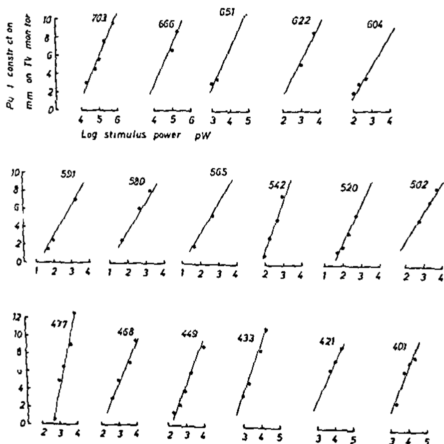


Fig 15 Individual pupil constriction data of a normal trichromat and the regression lines calculated These results constituted the basis of the spectral sensitivity curve shown in Fig 21 The results obtained with the 468 nm filter were deleted due to infrared leakage (see text)

The reproducibility of the method was checked by retesting one of the normal trichromat- This was done several months after the first session In Fig 13 (overleaf) the absolute criterion powers have been graphed In Fig 14, values obtained in the first session are plotted against thos from the second one

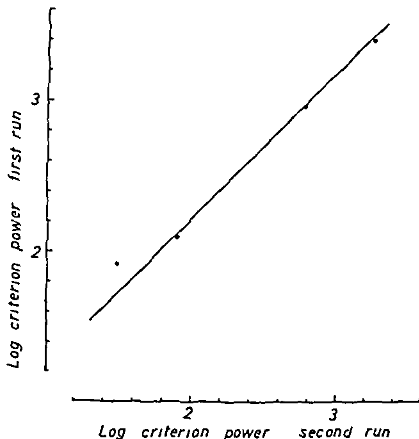


Fig 14 The criterion powers of the first session plotted against those obtained in the second one The line with slope 1 which best fits the points has been added by eye The overall sensitivity difference between the two runs is indicated by the fact that the line will cross the ordinate above the origin

For one normal trichromat response vs log stimulus power has been plotted in Fig 15 The calculated regression lines have been added The test stimuli used produced pupil constrictions of about 1-12 mm on the television screen The criterion response of this subject (4 8 mm) corresponded to the mid-range of the observed responses The spectral

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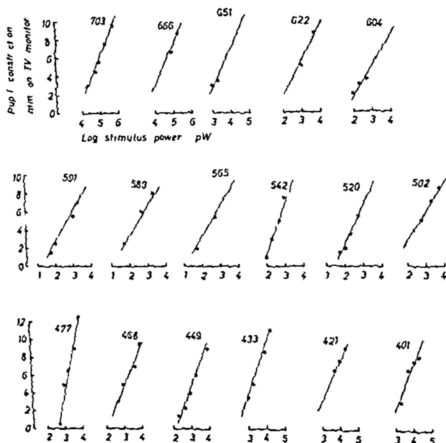


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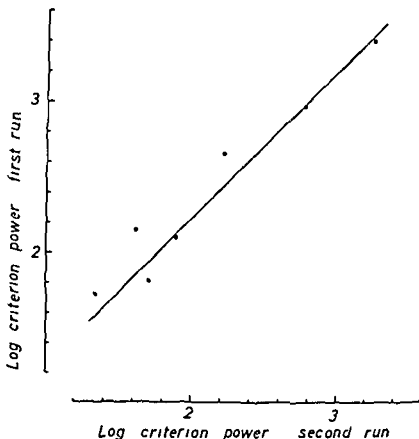


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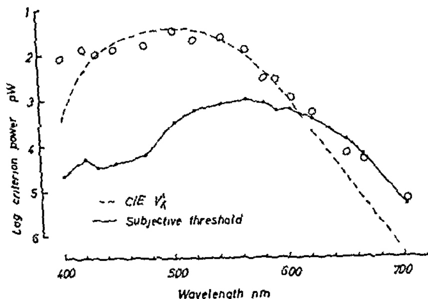


Fig 17 The dark-adapted foveal pupillomotor sensitivity of a normal trichromat The CIE V'_λ curve has been added to best fit in the medium and short wavelength regions and the subjective curve of the subject has been put to best fit in the long wavelength region

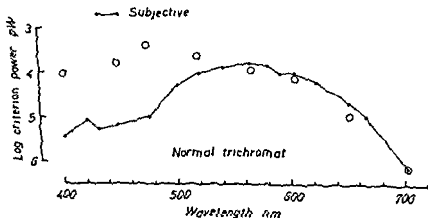


Fig 18 The pupillomotor spectral sensitivity of a normal trichromat recorded with a 0 1 cd/m^2 blue surround subtending about 45° The subjective spectral sensitivity of the subject has arbitrarily been put to the same height a 703 nm

The dark-adapted peripheral pupillomotor sensitivity is shown in Fig Here, like in the other pupillomotor diagrams, the absolute stimulus power in front of the eye constituted the ordinate values For comparison, the V'_λ curve has been added to the diagram and adjusted in height to best fit by eye

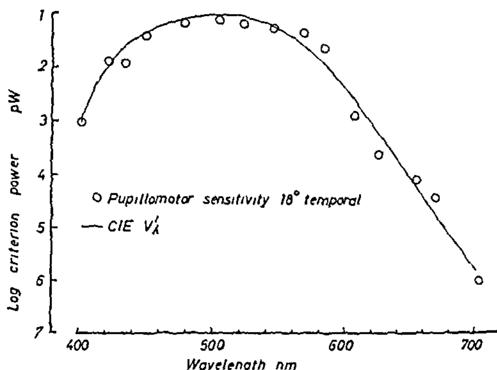


Fig 16 The 18° eccentric pupillomotor sensitivity of a normal trichromat The scotopic CIE V'_λ curve has been added and adjusted in height to best fit by eye

The dark-adapted foveal pupillomotor sensitivity is shown in Fig 17 The CIE V'_λ curve and the subjective spectral sensitivity of the subject have been added to the data These curves have been shifted vertically to fit the pupillomotor data in different spectral regions It is clearly seen that scotopic activity has heavily influenced the results Lack of correlation with the scotopic curve is seen for the red stimuli

The foveal pupillomotor spectral sensitivity with a 0 1 cd/m^2 blue surround is shown in Fig 18 It is evident that the surround was not sufficient to depress rod activity Steady-state pupil constriction was moderate and the pre-stimulation diameters about 6 mm

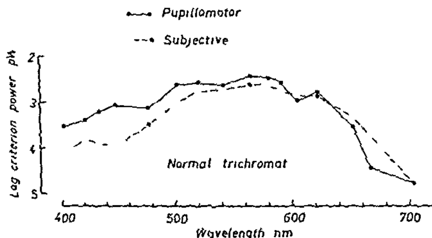


Fig 21 See text under Fig 19

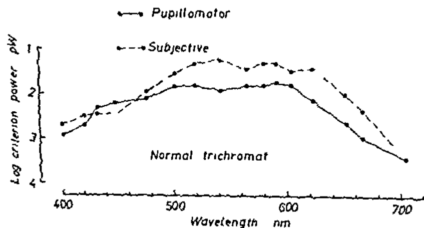


Fig 22 See text under Fig 19

The figures show that the overall pupillomotor spectral sensitivity varies between subjects The spread of the points of the average curve is thus considerable In order to eliminate the irrelevant information related to the overall sensitivity difference the following calculations were done For each subject the average criterion power of the 19 wavelengths was calculated This power value was considered the zero level of the subject The differences between the observed powers and the zero level were calculated for the 16 wavelengths For each wavelength the average of these differences was calculated and the values obtained made up the

Pupillomotor sensitivity at the cone plateau

The normal trichromats

The individual curves of the five normal trichromats are given in Figs 19-23 For comparison, the absolute threshold curve of each subject has bee[illegible] included and arbitrarily adjusted vertically to coincidence with the pupill[illegible] motor curves at 703 nm

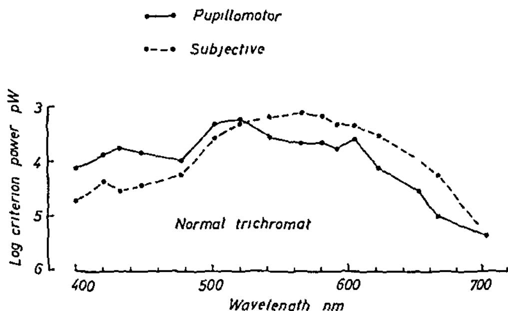


Fig 19 The pupillomotor spectral sensitivity of a normal trichromat recorded at the cone plateau of the dark-adaptation curve The subjective spectral sensitivity of the subject has been added and arbitrarily adjusted in height to coincidence at 703 nm

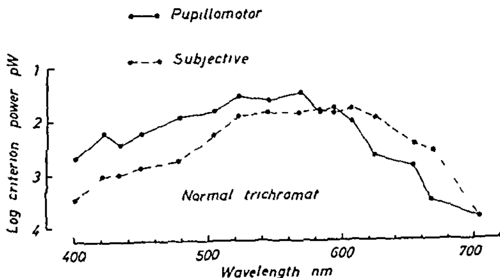


Fig 20 See text under Fig 19

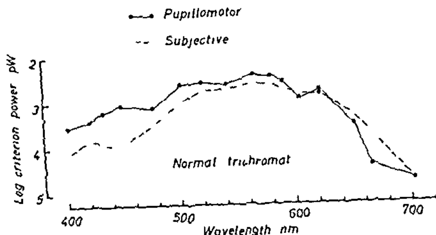


Fig 21 See text under Fig 19

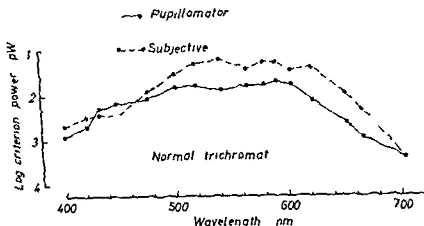


Fig 2 See text under Fig 19

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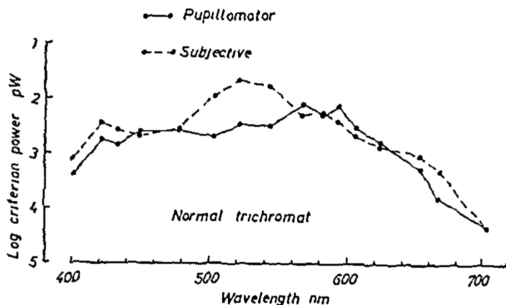


Fig 23 See text under Fig 19

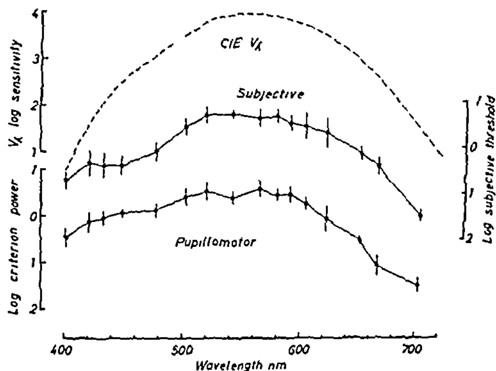


Fig 24 The average pupillomotor and subjective spectral sensitivities of the five normal trichromats The points are graphed in relation to the zero level discussed in the text Vertical lines show ± 1 S D The dashed line is the photopic CIE V_λ curve

average curve presented in Fig 24 with ± 1 S D The same calculations were performed with the subjective data The average subjective curve is also presented in Fig 24 The results of the two methods are similar pupillomotor sensitivity is however somewhat higher in the short wavelength region

In Fig 25 pupillomotor spectral sensitivity data of ALPERN & CAMPBELL (1962) and ALEXANDRIDIS & KOEPPE (1969) has been added to the average curve Correspondence is good except for the lower ALPERN & CAMPBELL sensitivity in the green

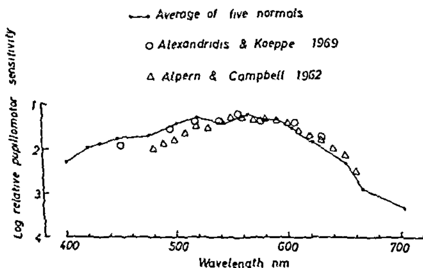


Fig 25 The average pupillomotor spectral sensitivity of the five normal trichromats and the photopic pupillomotor spectral sensitivity data presented by ALPERN & CAMPBELL (1962) and ALEXANDRIDIS & KOEPPE (1969) The data points have been shifted vertically to best fit with the curve

The colour defectives

The pupillomotor spectral sensitivity curves of the colour defectives are drawn in Figs 26 34 For comparison the figures also show the subjective spectral sensitivity of the subject and the average normal trichromat pupillomotor sensitivity The ordinate shows the absolute criterion powers of the pupillomotor respo se of the defective

The protanope data is shown in Figs 26 and 27 In the figures the curves have been vertically shifted to the same height at 401 nm (p 36)

The spectral sensitivity of the protanopes was reduced for wavelengths above 500 nm

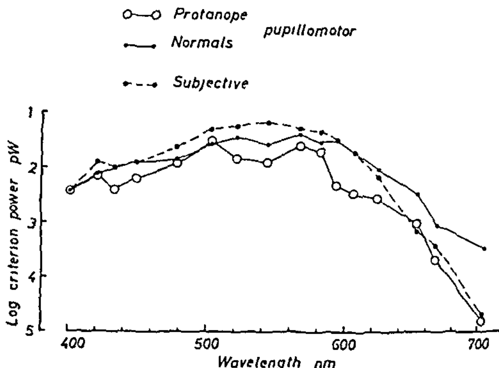


Fig 26 The pupillomotor spectral sensitivity of a protanopic subject recorded at the cone plateau of the dark-adaptation curve The subjective spectral sensitivity curve of the subject and the average curve of the normal trichromats have been added and vertically adjusted to the same height at 401 nm

The average pupillomotor curve of the normal trichromats and the subjective threshold curve of the deuteranopes have been equalized with the deuteranope pupillomotor response curves at 703 nm (p 37)

The pupillary responses of these two subjects are remarkable in that they show a broad sensitivity reduction in the mid-spectral region (Figs 28 and 29)

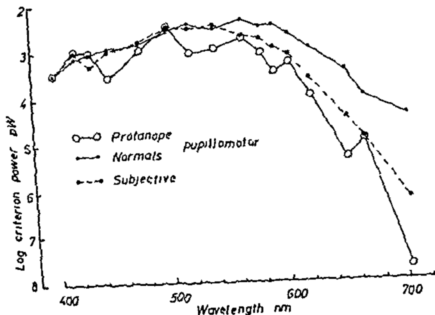


Fig 27 See text under Fig 26

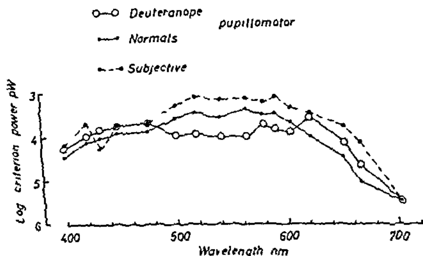


Fig 8 The pupillomotor spectral sensitivity of a deuteranopic subject recorded at the cone plateau of the dark-adaptation curve The subjective spectral sensitivity curve of the subject and the average curve of the normal trichromats have been added The curves have been shifted vertically to coincidence at 703 nm

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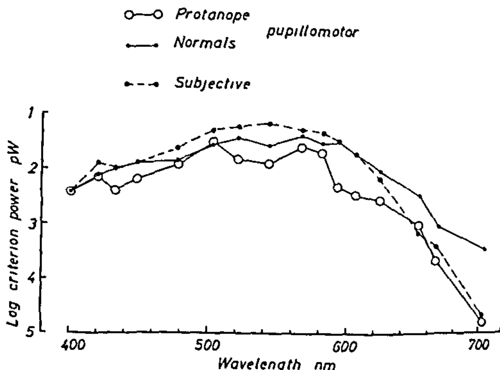
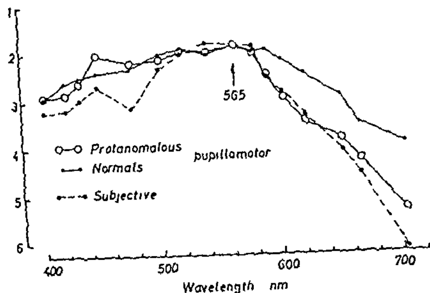


Fig 26 The pupillomotor spectral sensitivity of a protanopic subject recorded at the cone plateau of the dark-adaptation curve The subjective spectral sensitivity curve of the subject and the average curve of the normal trichromats have been added and vertically adjusted to the same height at 401 nm

The average pupillomotor curve of the normal trichromats and the subjective threshold curve of the deuteranopes have been equalized with the deuteranope pupillomotor response curves at 703 nm (p 37)

The pupillary responses of these two subjects are remarkable in that they show a broad sensitivity reduction in the mid-spectral region (Figs 28 and 29)



F g 31 See text under Fig 30

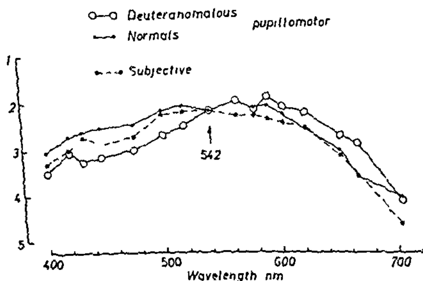


Fig 32 The pupillomotor spectral sensitivity of a deuteranomalous subject recorded at the cone plateau of the dark-adaptation curve The subjective spectral sensitivity curve of the subject and the average curve of the normal trichromats have been adju ted to fit the pupillomotor curve at 542 nm

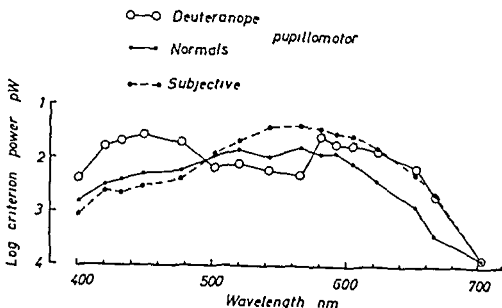


Fig 29 See text under Fig 28

The pupillomotor spectral sensitivity of the two protanomals was reduced in the long wavelength region (Figs 30 and 31) In the figures the curves are put to the same height at 565 nm (p 38)

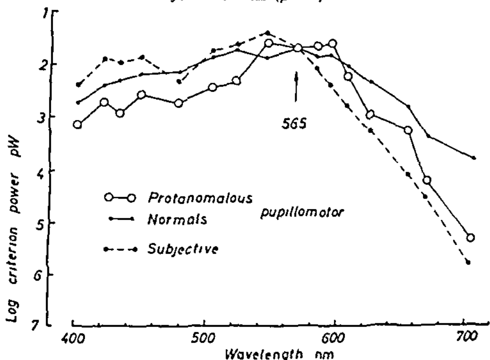


Fig 30 The pupillomotor spectral sensitivity of a protanomalous subject recorded at the cone plateau of the dark-adaptation curve The subjective spectral sensitivity curve of the subject and the average curve of the normal trichromats have been adjusted to fit the pupillomotor curve at 565 nm

DISCUSSION

THE ABSOLUTE THRESHOLD CURVES

Spectral sensitivity curves of normal trichromats (Figs 19-23) show irregularities with a hump at about 430 nm and small humps at 560-620 nm. The humps in the orange differ between subjects and are almost completely smoothed out in the average curve (Fig 7). The overall shape of the curve corresponds to that of other AT studies as shown in Fig 7 by comparison with the HSIA & GRAHAM (1957) curve. The blue hump is however more prominent in this study's curves. Compared with the V_λ curve (Fig 24) spectral sensitivity is higher at both spectral ends. As explained on p 11 this finding is considered a sign of chromatic channel contribution.

The spectral sensitivity of the two protanopes (Fig 8) is distinctly reduced in the long wavelength region. A similar reduction has been found in a number of studies in which the AT method or other subjective methods have been used (ABNEY & WATSON 1916, PITT 1935, WILLMER 1950, ZANEN et al 1957, BOYNTON et al 1959, GRÜTZNER 1962, WALD 1966, VERRIEST 1971 and others). For comparison the average protanope curve of HSIA & GRAHAM (1957) is included in Fig 8.

In deuteranopia (Fig 9) deviations from the average curve of normal trichromats are minor. There is a small sensitivity increase especially in the short wavelength region. This result may be a consequence of the equalization at 703 nm. The slight abnormalities found correspond to the minor deviations seen in PITT's (1935) HBM measurements. On the other hand short wavelength sensitivity reduction has been shown in several other studies (e g BOYNTON et al 1959, COLLINS 1959, GRÜTZNER 1962, WALD 1966, VERRIEST 1971). In Fig 9 the average deuteranope curve of HSIA & GRAHAM (1957) has been added for comparison.

Protanomals (Fig 11) show reduced sensitivity to wavelengths longer than that of the equalization point (565 nm). This result correlates well with a number of earlier studies of the subjective spectral sensitivity (WRIGHT 1946, GRÜTZNER 1962, VERRIEST 1971).

The deuteranomals (Fig 14) show increased short wavelength sensitivity, a finding not consistent with the assumed pigment absorption shift. Neither does it agree with earlier measurements in which the short wavelength

The results of the three deuteranomalous subjects are shown in Figs 32-34 The comparison curves have been brought to equal height with the pupil response curve at 542 nm (p 38)

Compared with the average curve of the normals, sensitivity is reduced below 542 nm Two of the subjects further show increased sensitivity for longer wavelengths

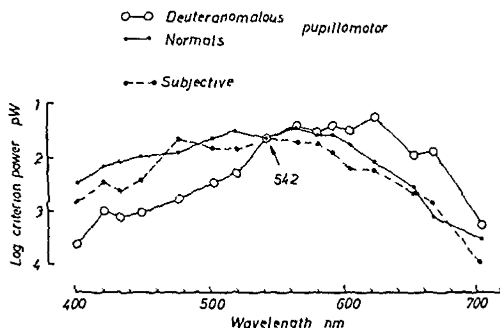


Fig 33 See text under Fig 32

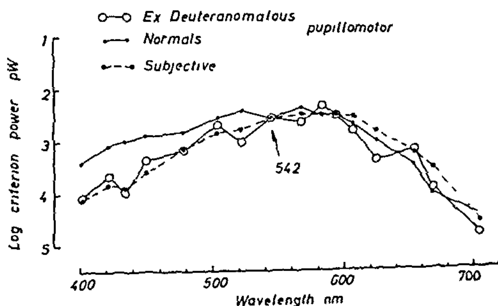


Fig 34 See text under Fig 32 This subject was an extreme deuteranomalous trichromat

D I S C U S S I O N

TFE ABSOLUTE THRESHOLD CURVES

Spe tral sensitivity curve. of normal trichromats (Figs 19-23) show irregularities with a hump at about 430 nm and small humps at 560-620 nm The humps in the orange differ between subjects and are almo t completely smoothed out in the average curve (Fig 7) The overall shape of the curve orresponds to that of other AT studies as shown in Fig 7 by comparison with the HSIA & GRAHAM (1957) curve The blue hump is however more prominent in this study s curves Compared with the V_λ curve (Fig 4) spectral sensitivity is higher at both spectral ends As explained on p 11 this finding is considered a sign of chromatic channel contribution

The spectral sensitivity of the two protanope (Fig 8) is distinctly reduced in the long wavelength region A similar reduction has been found in a number of studies in which the AT method or other subjective methods ha e been used (ABNEY & WATSON 1916 PITT 1935 WILLMER 1950 ZANEN et al 1957 BOYNTON et al 19 9 GRÜTZNER 1962 WALD 1966 VERRIEST 1971 and others) For compari on the average protanope curve of HSIA & GRAHAM (1957) is included in Fig 8

In d utera opia (Fig 9) deviations from the average curve of normal trichromats are minor There is a small sensitivity increase especially in the short wavelength region This result may be a cor equence of the eq alization at 703 nm The slight abnormalities found correspond to the minor deviations seen in PITT s (1935) HBM measurements On the other hand short wavelength sensitivity reduction has been shown in several other s udies (e g BOYNTON et al 1959 COLLINS 1959 GRÜTZNER 1962 WALD 1966 VERRIEST 1971) In Fig 9 the average deuteranope curve of HSIA & GRAHAM (1957) has been added for comparison

Protanom ls (Fig 11) show reduced sensitivity to wavelengths longer than that of the equalization point (65 nm) This result correlates well with a number of earlier studies of the subjective spectral sensitivity (WRIGHT 1946 GRÜTZNER 1962 VERRIEST 1971)

The deu eranomals (Fig 12) show increased short wavelength sensitivity a finding not consistent with the assumed pigment absorption shift Neither does it agree with earlier measurements in which the short wavelength

sensitivity has been found to be reduced (COLLINS 1959, GRÜTZNER 1962, VERRIEST 1971) COLLINS average deuteranomaly curve is shown in Fig 12 for comparison

THE PUPILLOMOTOR EXPERIMENTS

The relation between stimulus power and response amplitude

The pupillomotor spectral sensitivity was calculated from log stimulus power / response amplitude data obtained for each wavelength For small responses (not larger than 1-3 mm pupil constriction), a number of studies have shown a linear relation between log stimulus intensity and pupil constriction (STARK, TWEEL & REDHEAD 1962, LOWENSTEIN et al 1964, BOUMA 1965, SCHUBERT & THOSS 1967, WEBSTER 1969, KIETZMANN & GLIEM 1972 MUNSINGER & BANKS 1974) With larger responses the response curve levels off Deviation from the linear shape is also expected for very small responses The noise of the registration system often conceals these small responses but the deviation is evident in curves presented by LOWENSTEIN & LOEWENFELD (1959) and ALPERN et al (1974) Log stimulus intensity / response amplitude curves with stimuli of different angular subtense were recorded by WEBSTER COHEN & BOYNTON (1968) The slope was steeper in large angle curves The saturation or levelling off of the curve for larger responses was less evident with a small angle stimulus

The linear relation between response amplitude and log stimulus power shown in Fig 15 is good No levelling off is seen in any extreme of the range tested This result can probably be explained by the fact that only small responses were measured The small stimulus subtense also may have contributed to the absence of levelling off at high intensity (cf WEBSTER et al above)

As evident in Fig 15 the slope of the regression lines varied between wavelengths Slope variation has earlier been described both between wavelengths and between subjects (LOWENSTEIN et al 1964 BOUMA 1965 WEBSTER et al 1968 ALEXANDRIDIS & KOEPPE 1969) In Fig 15 it is seen that the slope did not change systematically with wavelength This finding was also noted in the results of the other subjects

A criterion respon e of 10 per cent of the average pre-stimulation diameter was chosen The criterion level affects the spectral sensitivity results when wavelength slope varies For some subject, the extrapolated zero response spectral sensitivity was drawn The shape of these curves differed considerably from that of the 10 per cent curves Different curve shape is also seen in some diagrams published by BOUMA (1965) in which the criteria were 0 mm 1 mm and 2 mm Because of the expected levelling off of the response curve near zero response it was not considered meaningful to use extrapolated power values The criterion chosen corresponded to the mid portion of the obtained re ponse range

The pre-stimulation diameters

The average pre-stimulation pupil diameter o the 14 subjects varied betwe n 48 and 82 mm on the television screen (these values about 10 times the actual diameter are given here because the scale factor was not determined for each subject) The total range of observed diameters was 36-86 mm For a single subject the pre-stimulation diameter varied maximally 32 mm; in most subjects the differences were not larger than 15 mm For a single wavelength the pre-stimulation diameter varied maximally 15 mm and ge erally about 5 mm

These figures are cited because it has been shown that the phasic light reflex may be influenced by the size of the pupil STARK (1964) showed that the response decreases with decreasing pupil diameter However no response differences were found by BOUMA (1965) within the 3-7 mm range Non-linearity of the pupil response to accommodative stimulation was shown by SEMMLOW HANSMANN & STARK (1975) The cause was shown to be non-linearity in the sphincter muscle action Because the shape of the gain/diameter curve was similar to that obtained for the light reflex (SEMMLOW & STARK 1973) a motor origin can reasonably be assumed for the light reflex divergence from linearity

For pupil sizes between 3 5 and 6 mm variations in re ponsiveness are limited to ± 10 per cent (SEMMLOW HANSMANN & STARK 1975) It follows that even in the extreme cases given above variations greater than ± 10 per cent are less likely It has not been possible to test for this error source However one can conclude from the spectral sensitivity curves that points obtained with pupil sizes greater or smaller than the average do not di tort the overall curve shape In Fig 31 e g the average pre-stimulation diameters at 421 nm and at 703 nm differed by 23 mm on the television screen

The slow variations in pre-stimulation diameter are assumed to be caused by fluctuations in the supranuclear control of the pupillomotor centers (p 21) A steadily increasing pupil constriction may be caused by increasi fatigue Such a constriction was not seen during the two hours a test serie lasted

A phenomenon that sometimes disturbed the test subjects was the appearance of a mist over the visual field The grey or coloured moving clouds appeared about 3-5 minutes after the end of light adaptation, i e simultaneously with the test minute They were sometimes accompanied by pupil constriction and oscillations necessitating retesting The phenomenon which lacks explanation has also been described by CRAWFORD (1936), BOUMA (1965) and HORNUNG (1966)

A possible error source are the small irregular pupil contractions calle pupillary unrest The frequency and amplitude of this unrest varies between individuals both increase with retinal illumination The major frequency component is in the frequency range of 0 05-1 cps The origin has been shown to be outside the light reflex loop (STARK, CAMPBELL & ATWOOD 1958, STARK 1959 1962) In the experiments of this study no significant unrest was noted during the continuous observations of the pupils

Rod intrusion and the cone plateau

In several studies, it has been shown that both rods and cones contribute to the phasic pupillary response Whether the one system or the other dominates the response is not of interest in this study However rod intrusion into photopic records is of interest because rod responses may interfere with cone responses even when strictly foveal stimulation is used

The problem is illustrated in the dark-adapted foveal response curve (Fig 17) This curve does not correspond to the photopic spectral sensitivity curve except in the red spectrum extreme It is most likely that peripheral rods have been stimulated by stray light as reported by ALPERN & CAMPBELL (1962) and BOUMA (1965) even though the stimuli used in the present study were of low intensity The pupillomotor centers cannot discriminate between focused foveal light and peripheral stray light Only when small near-threshold stimuli are used do the rods remain silent (SCHWEITZER 1956 LOWENSTEIN et al 1964)

Several methods have been used in attempts to suppress rods ALPERN & CAMPBELL (1962) and BOUMA (1965) used blue backgrounds and were able to record spectral sensitivity curves of photopic character The same procedure was tried in this study (Fig 18) but the luminance of the conditioning field (substantially lower than that of the authors above) was not sufficient for rod suppression The data points clearly deviated from the photopic curve shape However the main reason for not using this method after all was that it was considered u wise to u e chromatic adaptation in a s udy of spectral sensitivity in colour defectives A blue background bleaches short and medium wavelength pigments more than the long wavelength pigment e pecially if the background is of high luminance

Another possible method involves the use of a large white background This p ocedure was used by ALEXANDRIDIS & KOEPPE (1969) With a background of 7 cd/m^2 they obtained a spectral sensitivity curve similar to WALD s (1945) peripheral photopic curve Preliminary experiments with a similar background were performed in this study but abandoned due to the small os illating pupils obtained with the high intensity field

In this study testing at the cone plateau of the dark-adaptation curve was chosen as the method providing sufficient rod suppression and a steady large pupil WALD (1945) and SPERLING & HSIA (1957) used this principle in order to eliminate rod intrusion in studies of peripheral cone sensitivity The same method was recently used by STABELL & STABELL (1976) OHBA & ALPERN (1972) and ALPERN et al (1974) performed pupil experiments at the cone plateau

A prerequisite for the operation is knowledge of the temporal characteristics of bleaching and regeneration of rod and cone pigments These characteristics have been studied psychophysically and with the aid of fundus reflectometry and electroretinography The general kinetic equation of RUSHTON (1958 1963 196 b) has later been tested and found valid for different bleaching and regeneration conditions of rods and cones (ALPERN 1971 ALPERN MAASEIDVAAG & OHBA 1971 HOLLINS & ALPERN 1973)

The time constant of the exponential bleaching and regeneration functions varies in different studies Fundus reflectometry studies of the ed-green pigments have given values between 105 and 140 s (RUSHTON & HENRY 1958 RUSHTON 1963 1965 b ALPERN et al 1971 HOLLINS & ALPERN 1973) The rate of recovery of the blue pigment is said to be slightly lower (DU CROZ & RUSHTON 1966) The time constants of the pupillomotor dark adaptation curves of OHBA & ALPERN (1972) were 120 s (cones) and 400 s (rods) The

The slow variations in pre-stimulation diameter are assumed to be caused by fluctuations in the supranuclear control of the pupillomotor centers (p 21) A steadily increasing pupil constriction may be caused by increasing fatigue Such a constriction was not seen during the two hours a test series lasted

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average values reported by NORREN & PADMOS (1974) were 140 s for foveal blue recovery and 90 s for foveal red-green recovery (psychophysical measurements and electroretinography)

The values used in this study were 130 s (cones) and 400 s (rods) The cone time constant selected by this author is thus in the upper range of those reported If actual cone regeneration were faster there would be a higher fraction of regenerated cone pigments, and threshold differences between rods and cones would be larger x)

The accuracy of the calculations was tested by subjective adaptometry using the Goldmann-Weekers adaptometer and following the light-dark sequence given on p 32 It was found that the threshold curve in the dark levelled off after about 4 minutes and that the cone plateau remained at the same level from the first to the 17th run The last dark-adaptation period was continued into the scotopic phase, and it was found that the cone-rod break appeared after about 8 minutes The 4 min 36 s dark-adaptation was thus sufficient to bring cone adaptation onto the plateau after testing was completed, more than two minutes elapsed before the cone-rod break took place

The threshold sensitivity of the phasic pupil light reflex during dark adaptation follows that of the subjective sensitivity (ALPERN KITAI & ISAACSON 1959 ALPERN et al 1963 ALEXANDRIDIS 1968 1971 TRIMARCHI & BIANCHI 1976) After intense light-adaptation the pupil dilates in several phases (ALPERN & CAMPBELL 1963, BORGMANN 1967 NEWSOME 1971) After a full bleach of a large retinal area pupil diameter in the dark is linearly related to the fraction of regenerated rhodopsin (ALPERN & OHBA 1972) In the present study the redilatation time was shorter than the 5-30 minutes which had earlier been found necessary for full pupil dilatation This was the case because we did not want rhodopsin to regenerate to more than 80 per cent During the test minute the pupil remained fairly stable and variations during this minute were random and without systematic tendency toward dilatation

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x) Rhodopsin regeneration was assumed never to exceed 80 per cent This is to be compared with the results of RUSHTON (1961) and RUSHTON & POWELL (1972) which showed that scotopic vision took over from photopic when rhodopsin was regenerated to 92-93 per cent

Pupillomotor sensitivity curves

Test reproducibility

In one subject, good agreement was found between two runs separated by several months and numerous lamp output calibrations (Fig 14) In the retest sensitivity was overall higher than in the first run The absolute power differences amounted to maximally 0 5 log units However if the differences were related to a zero level, as discussed on p 47 the maximal difference was reduced to 0 3 log units

In Fig 15 data from the two tests have been plotted against each other The line with slope 1 which best fits the data points was fitted to the graph by eye There is good agreement between the points and the line which indicates that there was no systematic wavelength-dependent difference between the two runs The overall sensitivity difference is reflected from th fact that the line crosses the ordinate above the origin This finding corresponds to the day-to-day variation in overall responsiveness reported by BOUMA (1965)

The normal trichromats

Compared with the V_λ curve pupillomotor sensitivity is relatively higher in both spectral extremes (Fig 24) This indicates that the spectral sensitivity recorded with our method is influenced by chromatic-channel impulses as has been proposed for subjective AT and HBM results (WAGNER & BOYNTON 1972 GUTH & LODGE 1973) A comparison with the curves of KING-SMITH & CARDEN (1976) is of interest They found broad three humped threshold curves with a 1000 td background and a smooth (non opponent dominated) curve with a zero background Al o STILES & CRAWFORD (1934) SMITH KINNEY (1958) and SPERLING & HARWERTH (1971) found the humps more prominent with an added white background The shape of this study s curves may be due to the fact that the curves were obtained at the cone plateau i e in a state of relative light adaptation with an equivalent background corresponding to the amount of unregenerated receptor pigments

Ex ept for the overall sensitivity differences in the pupillomotor urves of the normal trichromats there are also differen es in the curve shape Possible causes are variations in ocular pigmentation and cone pigment density Red green pigment density variations have been shown by RU HTON & BAKER (1964) They fou d that subjects with extremely high and low

average values reported by NORREN & PADMOS (1974) were 140 s for foveal blue recovery and 90 s for foveal red-green recovery (psychophysical measurements and electroretinography)

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Except for the overall sensitivity differences in the pupillomotor curves of the normal trichromats there are also differences in the curve shape Possible causes are variations in ocular pigmentation and cone pigment density Red-green pigment density variations have been shown by RUSHTON & BAKER (1964) They ound that subje ts with extremely high and low

red-green brightness matches had correspondingly low and high ratios of erythrolabe/chlorolabe LEE (1966) and VERRIEST (1970) likewise found individual variations in the luminosity curves of normal trichromats

The overall shape of the pupillomotor curves is similar to that of the subjective absolute threshold curves except for a somewhat higher relative sensitivity in the short wavelength domain There are several possible reasons for the higher sensitivity in the blue One is rod intrusion however, this is unlikely considering the figures on rod regeneration and the subjective adaptometry Another is stray light stimulation of parafoveal cones There is no reason (except for the STILES-CRAWFORD effect) why not cones as well as rods should be activated by stray light It has been shown that the peripheral cone sensitivity is relatively higher in the short wavelength region (see HEDIN 1977) A third reason also possible is a relatively higher contribution of the blue mechanism to the pupillomotor curves than to the subjective curves A fourth reason is a different rate of recovery of the cone pigments However as discussed on p 59, blue pigment recovery is considered somewhat slower than that of the red-green pigments If of any significance, this difference should reduce the prominence in the blue

The blue humps seen in this study s curves correspond to those seen in earlier subjective studies and in the AT curves of the subjects Blue humps are seen in LAURENS (1923) pupillomotor spectral response curves they were assumed to depend upon fluorescence in the eye media This study s blue humps correspond to a blue mechanism with maximum at about 440 nm, they are thus consistent with the blue mechanism reported in the literature (p 7)

A possible cause of irregularities in the blue spectrum region is macular pigment absorption (WALD 1945) The absorption curve of this pigment is multihumped with maximum at about 460 nm The shape and wavelength maximum of the blue humps found in this study make a significant contribution from the macular pigment unlikely

The irregularities around 600 nm vary between subjects They are smoothed out in the average curve there is a tendency to formation of two humps at 520 nm and 570 nm however The hump with maximum at about 610 nm reported in several subjective threshold studies (HSIA & GRAHAM 1957 SPERLING & LEWIS 1959 SPERLING & HARWERTH 1971 and others) is not seen

As discussed on p 11 various theories have been put forward concerning the relation between the cone mechanism spectral sensitivities and the luminosity curve These include the views that the luminosity curve depends on the upper envelope of the fundamentals (the pigment sensitivity which is highest STILES & CRAWFORD 1934) or the weighted sum of the spectral sensitivities (WALD 1964) or on subtractive interactions (SPERLING & HARWERTH 1971)

The shape of the pupillomotor curves does not give a definite clue as to the relation between these curves and the cone mechanisms The blue hump correspond to the upper envelope of a blue mechanism The smoothness in the green to-red region makes a subtractive interaction unlikely Attempts were made to derive the green and red mechanisms from the sensitivity (threshold power $^{-1}$) differences between normals and dichromats In this manner irregular curves were obtained with maxima in the green (at about 535 nm) and yellow (at about 575 nm) Owing to the irregularity of the curves they have not been reproduced However like the alterations found in the dichromats these curves fit better in a sum luminosity curve than in a SPERLING-type interaction curve

Earlier attempts to measure the photopic pupillomotor spectral sensitivity have been hindered by rod intrusion and few purely photopic curves have been presented The steady state curve of LAURENS (1923) was an equal-response curve with good agreement to the subjective luminous sensitivity ALPERN & CAMPBELL (1962) used an intense blue background and found a pupillomotor spectral sensitivity curve in agreement with the photopic luminous sensitivity They measured the power equivalent to a threshold pupillary reaction Short wavelength sensitivity is lower in ALPERN & CAMPBELL s data than in this study s curves (Fig 25) possibly becau e of selective chromatic adaptation Comparisons in the blue spectral region are not possible because measurements were not done below 480 nm

BOUMA (1965) also used an intense blue background but obtained the spectral sensitivity curve from stimulus power/response data BOUMA s filters were broad banded and only six wavelengths were tested Low short wavelength sensitivity is not seen in BOUMA s curve

The spectral sensitivity obtained at eight wavelengths by ALEXANDRIDIS & KOEPPE (969) corresponds to this study s results (Fig 25) These authors measured the luminance necessary for a given pupillary response A high luminance white background was used for rod suppression This method was abandoned by this author after preliminary experiments

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A possible cause of irregularities in the blue spectrum region is macular pigment absorption (WALD 1945) The absorption curve of this pigment is multihumped with maximum at about 460 nm The shape and wavelength maximum of the blue humps found in this study make a significant contribution from the macular pigment unlikely

The irregularities around 600 nm vary between subjects They are smoothed out in the average curve there is a tendency to formation of two humps at 520 nm and 570 nm however The hump with maximum at about 610 nm reported in several subjective threshold studies (HSIA & GRAHAM 1957 SPERLING & LEWIS 1959 SPERLING & HARWERTH 1971 and others) is not seen

As discussed on p 11 various theories have been put forward concerning the relation between the cone mechanism spectral sensitivities and the luminosity curve The e include the views that the luminosity curve depends on the upper envelope o the fundamentals (the pigment sen.itivity which is highest STILES & CRAWFORD 1934) on the weighted sum of the spectral sensitivities (WALD 1964) or on subtractive interactions (SPERLING & HARWERTH 1971)

The shape of the pupillomotor curves does not give a definite clue as to the relation betw en these curves and the cone mechanisms The blue hump corresponds to the upper envelope of a blue mechanism The smoothness in the green to-red region makes a subtractive interaction unlikely Attempts were made to derive the green and red mechanisms from the sensitivity (threshold power $^{-1}$) differences between normals and dichromats In this manner irregular curves were obtained with maxima in the green (at about 535 nm) and yellow (at about 575 nm) Owing to the irregularity of the curves they have not been reproduced However like the alterations found in the dichromats these curves fit better in a sum luminosity curve than in a SPERLING-type interaction curve

Earlier attempts to measure the photopic pupillomotor spectral sensitivity have been hindered by rod intrusion and few purely photopic curves have been presented The steady-state curve of LAURENS (1923) was an equal-response curve with good agreement to the subjective luminous sensitivity ALPERN & CAMPBELL (1962) used an intense blue background and found a pupillomotor spectral sensitivity curve in agreement with the photopic luminous sensitivity They measured the power equivalent to a threshold pupillary reaction Short wavelength sensitivity is lower in ALPERN & CAMPBELL s data than in this study s curves (Fig 25) possibly because of selective chromatic adaptation Compari.ons in the blue spectral region are not possible because measurements were not done below 480 nm

BOUMA (1965) also used an intense blue background but obtained the spectral sensitivity curve from stimulus power/response data BOUMA s filters were broad banded and only six wavelengths were tested Low short wavelength sensitivity is not seen in BOUMA s curve

The spectral sensitivity obtained at eight wavelength by ALEXANDRIDIS & KOEPPE (1969) corresponds to this study s results (Fig 25) These authors measured the luminance necessary for a given pupillary response A high luminance white background was used for rod suppression This method was abandoned by this author after preliminary experiments

red-green brightness matches had correspondingly low and high ratios of erythrolabe/chlorolabe LEE (1966) and VERRIEST (1970) likewise fo nd inoividual variations in the luminosity curves of normal trichromats

The overall shape of the pupillomotor curves is similar to that of the subjective absolute threshold curves except for a somewhat higher relative sensitivity in the short wavelength domain There are several possible reasons for the higher sensitivity in the blue One is rod intrusion, however, this is unlikely considering the figures on rod regeneration and the subjective adaptometry Another is stray light stimulation of parafoveal cones There is no reason (except for the STILES-CRAWFORD effect) why not cones as well as rods should be activated by stray light It has been shown that the peripheral cone sensitivity is relatively higher in the short wavelength region (see HEDIN 1977) A third reason also possible is a relatively higher contribution of the blue mechanism to the pupillomotor curves than to the subjective curves A fourth reason is a different rate of recovery of the cone pigments However as discussed on p 59 blue pigment recovery is considered somewhat slower than that of the red-green pigments If of any significance this difference should redu e the prominence in the blue

The blue humps seen in this study s curves correspond to those seen in earlier subjective studies and in the AT curves of the subjects Blue humps are seen in LAURENS (1923) pupillomotor spectral response curves they were assumed to depend upon fluorescence in the eye media This study s blue humps correspond to a blue mechanism with maximum at about 440 nm they are thus consistent with the blue mechanism reported in the literature (p 7)

A possible cause of irregularities in the blue spectrum region is macular pigment absorption (WALD 1945) The absorption curve of this pigment is multihumped with maximum at about 460 nm The shape and wavelength maximum of the blue humps found in this study make a significant contribution from the macular pigment unlikely

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Protanomals (Figs 30 and 31) are assumed to have an abnormal red pigment with its spectral absorption shifted towards the green pigment Using the curve equalization described on p 38 the protanomals are shown to have reduced sensitivity for all wavelengths above the equalization point The deviation is similar to that found with the subjective method and agrees with the assumed pigment absorption shift Differences between the results of the two protan groups are small and that corresponds to findings in earlier subjective studies (GRÜTZNER 1962 VERRIEST 1971)

Only one protanomalous subject has been found in the pupillomotor literature (ALPERN & CAMPBELL 1962) This subject showed reduced red sensitivity by 0 4 log units at 625 nm This difference is lower than that found in this study Because no sensitivity curve or other details are provided the reason for the low difference is obscure

Deuteranopes pupillomotor curves (Fig 28 and 29) show the most surprising result of this study - a sensitivity loss in the mid-spectral region Earlier subjective deuteranope data is contradictory In some studies (PITT 1935 WILLMER 1950) differences to normals are insignificant In several others deuteranopes show reduced short wavelength sensitivity (HSIA & GRAHAM 1957 ZANEN et al 1957 BOYNTON et al 1959 GRÜTZNER 1962 VERRIEST 1971 POKORNY & SMITH 1972) In COLLINS (1959) AT study deuteranopes sensitivity loss is greatest in the mid spectral region but covers the whole region from the violet end to 620 nm Also the electrophysiological measurements of deuteranopes are contradictory in showing either a short wavelength sensitivity reduction or no deviation from the normal response

The subjective luminosity curves of the two deuteranopes of this study differ only slightly from the average normal curve

In the literature on pupillary spectral sensitivity different results are reported In several studies deuteranopes reactions did not differ from those of normals (steady-state ENGELKING 1922; phasic: ABELSDORFF 1900 b HESS 1915) But MORONE & CITRONI (1967) found a reduced response amplitude with a blue stimulus (only three wavelengths were tested) And ALRIAN (1973) using individually adjusted equal-luminance mesopic stimuli noted that in one deuteranope the pupil was slightly larger with stimuli in the mid spectral region

This study s results can be explained by the supposed deficiency of

BANKS & MUNSINGER (1974) only used two stimulus intensities at each of seven wavelengths A white background was used to suppress the rods Their spectral sensitivity curves are, compared with the V_λ curve, displaced towards shorter wavelengths It is interesting to note that they measured the direct pupil reaction with stimuli of 600 ms and 1200 ms These stimul durations exceed the latency of the pupil light reflex (200-500 ms, LOEWENFELD 1966) thus a reduction in stimulus power as a result of pupil constriction cannot be excluded

COHEN & SAINI (1977) used field alternation to suppress the rods They obtained a spectral response curve which is not totally free from rod intrusion The equal-energy design of that curve also made possible errors caused by non-linearities in the motor response However, 22 wavelengths were tested, and the curve shows a hump at about 510 nm These authors have stated that protracted studies contribute to data variability due to long-term pupil drift In order to exclude this possibility the first presented wavelength was tested again in some subjects in the end of our test series The differences in log criterion power which were found did not exceed 0 3 log units

T h e c o l o u r d e f e c t i v e s

Owing to the difference between subjects in overall pupillomotor sensitivity no attempts have been made to measure the absolute sensitivity deficiencies of the colour defectives Instead the vertical adjustments discussed on p 36-38 were made to increase clarity

The pupillomotor curves of the protanopes (Fig 26 and 27) show reduced long wavelength sensitivity the curves fall off steeply above 500 nm The difference as compared to normals is of the same order as in the subjective measurements The results correspond to the generally held opinion that the protanopes lack the red cone pigment They also agree with a number of subjective and electrophysiological spectral sensitivity studies (p 15)

In the few earlier pupillomotor studies of colour defectives most of the subjects have been protanopes Many studies were performed with a primitive apparatus and were limited to a few wavelengths The results in protanopes agree with those of this study in showing reduced sensitivity to red light (steady-state ENGELKING 1922 ADRIAN 1973; phasic: ABELSDORFF 1900 b HESS 1915 MORONE & CITRONI 1967)

SUMMARY

A review is given of the current knowledge of colour vision physiology especially the spectral sensitivity functions of the cones and the relation between the cone mechanisms and the overall spectral sensitivity curve The pathophysiology of colour vision deficiencies and the abnormalities found in the luminosity curves of red green congenital colour defectives are discussed

For objective measurement of the spectral sensitivity one can use electrophysiological methods or the registration of the pupillary light reflex Photopic pupillomotor spectral sensitivity curves are easily disturbed by rod intrusion caused by scattered light In the few earlier studies on this subject rods have been suppressed with high intensity white or blue backgrounds The curves obtained have shown similarity with the subjective luminosity function The number of colour defectives studied is small and the results are inconclusive

n the present study the pupillomotor and subjective spectral sensitivities of five normal trichromats and nine red-green congenital dyschromats were measured The colour vision diagnosis was made with the aid of a battery of colour vision tests An apparatus for the registration of the subjective absolute thresho d to 42 foveal stimuli was constructed 16 narrow-bandwidth interference filters in the spectral range 401-703 nm were used The 0 per cent thresholds were obtained from frequency-of-seeing curves In normal trichromats the curves recorded agreed with earlier published absolute threshold curves Protans differed from normals showing reduced long wavelength sensitivity The deutan subjects showed only minor discrepancies from the normal trichromats

The consensual pupillary light reactions were measured with an infrared television system For light stimulation an optical system was used which provided 1° foveal stimuli of predetermined power The interference filters used were identical with those of the subjective study

Linear regression lines were calculated from linear response / log stimulus power data The spectral sensitivity curves were constructed using a criterion response in the mid range of the respo ses recorded Preliminary experiments showed serious rod intrusion in full dark adaptation and with a low intensity blue background For rod suppression a procedure with

green receptors if it is assumed that cone responses rather than activity in non-opponent or opponent cells dominate the overall sensitivity curve The results thus support the opinion put forward on p 63 namely that the pupillomotor curve is made up of the (weighted) sum of cone responses Maximal difference between normal and deuteranope data is at about 535 nm This wavelength corresponds to the maximum sensitivity of the green mechanism (p 9) The blue hump is clearly visible in the deuteranope curves Blue cones evidently contribute more to the sensitivity curve than is expected on the basis of psychophysical experiments (WALD 1964, WALRAVEN 1974) and cone proportion measurements (MARC & SPERLING 1977)

In deuteranomaly the spectral absorption of the green pigment is assumed to be shifted towards longer wavelengths In earlier subjective studies, abnormalities of the luminosity curve have been found which are consistent with this shift (COLLINS 1959 GRÜTZNER 1962, VERRIEST 1971) A similar result was obtained in the pupillomotor curves of the three deuteranomals of this study (Figs 32-34) Only one of them however had reduced subjective sensitivity with the absolute threshold method The pupillomotor curve of the extreme deuteranomalous subject does not differ more from normality than the other two deuteranomalous curves

The available literature on spectral pupillary responses does not include any reports on deuteranomals

C O N C L U S I O N S

The aim of the study was to evaluate the possibility of using the pupil light reflex for objective colour vision testing The results show that measurements of the photopic spectral sensitivity with this procedure effectively disclose congenital red-green colour vision deficiencies

In pupillometry like in electrophysiological measurements a relatively complicated set-up is necessary In addition rod intrusion from scattered light makes the test situation more difficult On the other hand pupillometry is objective and less demanding on the observer than subjective methods Moreover it appears that more information can be obtained with this method of spectral sensitivity measurements than with other objective and subjective methods

S U M M A R Y

A review is given of the current knowledge of colour vision physiology especially the spectral sensitivity functions of the cones and the relation between the cone mechanisms and the overall spectral sensitivity curve. The pathophysiology of colour vision deficiencies and the abnormalities found in the luminosity curves of red green congenital colour defectives are discussed.

For objective measurement of the spectral sensitivity one can use electrophysiological methods or the registration of the pupillary light reflex. Photopic pupillomotor spectral sensitivity curves are easily disturbed by rod intrusion caused by scattered light. In the few earlier studies on this subject rods have been suppressed with high intensity white or blue backgrounds. The curves obtained have shown similarity with the subjective luminosity function. The number of colour defectives studied is small and the results are inconclusive.

In the present study the pupillomotor and subjective spectral sensitivities of five normal trichromats and nine red-green congenital dyschromats were measured. The colour vision diagnosis was made with the aid of a battery of colour vision tests. An apparatus for the registration of the subjective absolute threshold to 42' foveal stimuli was constructed. 16 narrow-bandwidth interference filters in the spectral range 401-703 nm were used. The 50 per cent thresholds were obtained from frequency-of-seeing curves. In normal trichromats the curves recorded agreed with earlier published absolute threshold curves. Protans differed from normals showing reduced long wavelength sensitivity. The deutan subjects showed only minor discrepancies from the normal trichromats.

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D E F I N I T I O N   O F   T E R M S

Ab olute threshold The absolute threshold of a visual stimulus is the power (or energy) necessary for just detecting the stimulus against a dark background It is often defined as the power equivalent to detection in 50 per cent of the presentations

Absorption spectrum The spectral absorption of light in the photopigments

Action spectrum The cone action spectra show the reactions of the cones to spectral stimuli These functions show the power (or energy) necessary to provoke a certain response

Brightness matching is the test condition in which two juxtaposed fields are adjusted in radiance to equal brightness When the fields are of different hue the test is called heterochromatic brightness matching

Central blue-blindness The tritan character of the central 20 of the fovea was described by WILLMER & WRIGHT (194) WALD (1967) showed that blue sensitivity is almost absent in the central 7-8 and increases rapidly towards the periphery Macular pigment absorption cannot account for the blue loss because the pigment is low in density in the foveal center It thus seems likely that the number of blue cones decreases towards the fixation point Recently this hypothesis has been confirmed in preparations of the baboon retina (MARC & SPERLING 1977)

Colour diagram Colours of different hue and saturation can be graphed in a colour diagram One such diagram is that of the XYZ chromaticity system in which colours are given the chromaticity coordinates x and y (Fig 35) Here the spectral wavelengths are arranged along the curved line The line of purple colours joins the points at the spectral ends All colours are located within these two lines

Colour matching involves the comparison of two juxtaposed fields of different wavelength composition and the adjustment of one or both of the fields to subjective identity Most often one field is made up of a certain number of fixed primaries The radiance of the primaries is adjusted so that their mixture is seen identical with the test field Curves showing the proportion of the primaries are called colour mixture functions

repeated light and dark adaptation was worked out Testing was performed at the cone plateau of the dark-adaptation curve The curves thus obtained from the normal trichromats showed agreement with the absolute threshold curves Spectral sensitivity was high in the spectrum extremes and there was a prominent blue hump as well as irregularities around 600 nm Pupillomotor sensitivity as compared with the subjective sensitivity was somewhat higher in the short wavelength region

The protan subjects showed a distinct long wavelength sensitivity reduction similar to that found in subjective studies No differences between the protanopes and the protanomals were seen The curves of the deuteranomalous subjects showed a shift in spectral sensitivity towards longer wavelengths The sensitivity of the deuteranopes was distinctly reduced in the mid-spectral region The findings in the deutan subjects are in accordance with the assumed pigment abnormalities in these conditions Corresponding abnormalities were not seen in the subjective curves The deviations seen in the pupillomotor curves indicate that the spectral sensitivity recorded in this manner is the sum of the (weighted) cone responses

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Cone fundamentals or cone mechanisms are the different kinds of cones with their characteristic action spectra

Cone pigments The light absorbing pigments in the outer segments of the cones

Confusion lines Colours located on the confusion lines of a colour diagram are perceived by colour defectives to be of identical hue The confusion lines of one type of colour vision deficiency are shown in Fig 35 The confusion line which joins the neutral point (in the center of the diagram) and the neutral spectral zone is called the neutral axis

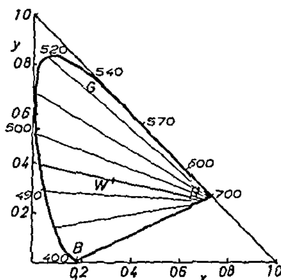


Fig 35 The XYZ colour diagram The confusion lines of protanopes are added

DARTNALL standard DARTNALL (1953) proposed that the absorption curves of photopigments have the same shape on a wavenumber axis LE GRAND (1972) STILES & WYSZECKI (1974) and others have shown that colour matching data cannot be transformed to three fundamentals which agree with the DARTNALL standard unless some impossible demands are met Direct pigment absorption spectra especially that of the long wavelength pigment are narrower than the DARTNALL standard

Difference spectra These curves show the difference in spectral absorption in the photopigments before and after bleaching

Hue is the term for subjective colour perception which corresponds to the dominant wavelength of the stimulus

rem nt threshold is the stimulus power necessary for threshold detection a ainst a white or coloured background

R sponse spectrum denotes the magnitude of the reactions to stimuli of equal power (or energy)

S ration describes the extent to which a colour differs from white The saturation threshold is the minimum amount of spectral radiance which has to be added to a neutral field in order that the mixture be perceived as non white

STILES π functions STILES (1939 1949 1959) measured the threshold power of a foveal spectral stimulus on a background of another wavelength at various radiance levels The method was called the two-colour threshold method The spectral characteristics of several cone functions were calculated They were called π-functions Three of them had their maximum in the short wavelength domain (π_1 π_2 π_3) two in the middle of the spectrum (π_4 π_4) and two in the long wavelength region (π_5 π_5) These functions have been repeatedly used as a reference for other measurements The curves are substantially influenced by the cone pigments but are not simple representations of the cone action spectra (ENOCH 1972)

Wavel ngth discrimination The ability to distinguish stimuli of different wavelength composition, The wavelength discrimination threshold is the minimum wavelength difference necessary for di crimination The equivalent term in subjective colour perception is hue discrimination

A C K N O W L E D G E M E N T S

Professor Björn Tengroth initiated this study and supported its realization

Research engineer Anders Glansholm gave invaluable intellectual and technical assistance during the experiments

Associate professor Lars Frisen Daniel Epstein, MD and many others helped the author under various phases of the work

All test subjects patiently accepted many hours of experiments

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R E F F R E N C E S

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SUPPLEMENTUM 136

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by

Norbert Lauinger

SCRIPTOR COPENHAGEN 1978

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Supplementum

BEUGUNGSGITTER AUF GRENZFLÄCHEN DES OPTISCHEN SYSTEMS DES MENSCHLICHEN AUGES

VON

NORBERT LAUINGER

Auf den sphärischen Grenzflächen des optischen Systems des menschlichen Auges sind Epithelzellen in Dichtestpackung vorwiegend als 1 Zell-Lagen *Flächenepithelien* eingelagert. Die Zellgrenzstrukturen weisen in Aufsicht poly- bzw. hexagonale Feldstrukturen mit Feldmittenabständen im µm-Bereich auf. Ihre Interpretation als Amplituden- und/oder Phasengitter muss aufgrund der Gitterkonstanten-Massperiodizitäten als naheliegend betrachtet werden. Der Beitrag der auf sphärischen Grenzflächen vor der Netzhaut eingelagerten Beugungsgitter zur optischen Abbildung kann lediglich in einem Einfluss auf das Fraunhofersche Beugungsbild bestehen, das in der *Fokusebene* des optischen Systems, also im Fernbereich dieser Gitter zustandekommt. Wenn jedoch auch die Netzhaut, *die ebenfalls aus der Invagination eines Flächenepithels entsteht*, als in die Fokusebene *eingelagertes* Beugungsgitter bzw. mit einer oder beiden Grenzmembranen *als Einfach-* oder *Doppelraster* interpretiert werden darf, so muss *ihr Beitrag* zur optischen Signalverarbeitung in direktem Bezug zu den ihr unmittelbar nachgelagerten Rezeptoren (Zapfen und Stäbchen) gesehen werden. In einer Gitter-Rezeptoren-Kombination, bei *der die Photorezeptoren* im Nahbereich des Gitters eingelagert sind, besteht die *Möglichkeit der* Frequenzanalyse in den diskreten *Fresnelschen* Interferenzebenen hinter dem Gitter. Die hierfür *gültigen Gesetzmässigkeiten* werden beschrieben und eine Modellrechnung für die *photoptische Frequenzanalyse* auf der Grundlage histologischer und funktioneller Netzhautdaten vorgestellt.

Key words: gitter-optik – flächenepithelien – gitter-rezeptoren-kombination – frequenzanalyse

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Key words: gitter – optik – flächenepithelien – gitter-rezeptoren-kombination – frequenzanalyse

I t d n D mark by B gtrykk t Fo m C p h g

z T bis zu 45 µm in der mittleren Schicht ca 15–20 µm in der innersten basalen Zellage ca 10 µm Im Hornhautendothel ca 18–20 µm im Linsen epithel im Linsenscheitel 11–14 µm randwärts reduzieren sich die Masse auf 5–10 µm In der Pigmentepithelschicht besitzen die hexagonalen Einzelzellen im hinteren Pol des Auges eine Breite von ca 12 µm die peripherwärts bis auf ca. 60 µm ansteigt Da die Zellabstandsmasse durchwegs oberhalb der Masse der im sichtbaren Spektralbereich verarbeiteten Lichtwellenlängen (0 4–0 8 µm) liegen dürfen wir arbeitshypothetisch die Flächenepithelien als beugende Strukturen als 2 dimensionale Flächen Beugungsgitter interpretieren die Zellabstandsmasse als Gitterkonstanten bezeichnen

Worin wäre die Rolle von aus Flächenepithelien gebildeten Beugungsgittern – zunächst unabhängig davon ob sie Phasen oder Amplituden oder Amplituden Phasen Strukturen darstellen – im optischen Abbildungsprozess in die Netzhaut Bildebene zu sehen wenn dabei die bewährten geometrisch optischen Gesetzmässigkeiten gültig bleiben sollen? Die Netzhaut Bildebene liegt im



Fig 1

Fr ut I t hes Beugung bild im Fernbereich eines hexag nalen Amplituden *Flächen* g tter be punktf rn ger l htq elle (G tterkonstante 0 m) Die O *Beugungs* rdnung st stark überbelichtet

Sa tl che hex gonale G tter über die *hier berichtet wird*, entstanden über d e ver kl nernde Abb ld ng von Vorlagen a f h chauflösende *Phot*graphische Platten oder F lme

1 Flachenepithelien auf spharischen Grenzflachen des optischen Systems des menschlichen Auges poly bzw hexagonale Beugungsgitter

Das auf die Netzhaut fokussierend abbildende optische System des menschlichen Auges stellt ein zentriertes System brechender Kugelflachen mit einer Aperturblende dar Der geometrischen Optik genugt diese Modellvorstellung um uber die als homogen behandelten auf spharischen Flachen begrenzten Medien die geometrisch optische Strahlenfuhrung und ihre Abbildungsgesetzmässigkeiten zu berechnen Die Elektronenmikroskopie hat die Vorstellung von der Medienhomogenität in Hornhaut Linse und Netzhaut widerlegt ohne deshalb die geometrisch optischen Abbildungsgesetze erschuttern zu mussen Sie hat weiterhin Daten geliefert zu den Flächenepi und endothelien die die sphärischen Grenzflachen des optischen Systems in der Embryonalentwicklung zunachst ausbilden und spater bedecken (Hornhautepi und endothel Linsenepithel Pigmentepithel)

Flachenepithelien sind gekennzeichnet als in nur einer Zellage in Dichtestpackung aneinandergelagerte prismatische Einzelzellraume Die Ausbildung eines Epithels seine Invagination (bei Linse und Netzhaut) und seine Ausformung auf spharischen Mantelflachen ist ein in der organismischen Morphogenese oft geubter und sicher ablaufender Prozess Er fuhrt zu einigen in nur geringen Abwandlungen wiederkehrenden Formmerkmalen der Flachenepithelien

Zellkorper die durch Dichtestpackung auf Grenzflachen aneinandergelagert werden bilden regelmassige prismatische Zellgrenzstrukturen aus d h ihre Grundflächen nehmen im Querschnitt poly uberwiegend hexagonale Form an ihre Seitenflachen und kanten orientieren sich senkrecht zur spharischen Standflache

Im Zenith oder am aquatorialen Rand einer Epithelschicht ergibt es sich unter den konzentrischen Einflussen eines Stoffwechselfeldes oder des Drucks vom Rand her appositionell nachwachsender neuer Zellkorper sehr leicht dass die Zelldichte entweder zum Zenith oder umgekehrt zum Rand der spharischen Flache hin in ebenfalls nahezu konzentrischen Zonen zu bzw abnimmt In Zonen grosserer Zelldichte langen sich die Zellkorper und ihre prismatischen Querschnittsflachen werden reduziert Damit verkleinert sich auch der Abstand zwischen Zellgrundflachen und das Verteilungsmuster der Zellquerschnittsflachen nahert sich dem Bild einer radialkonzentrischen hexagonalen Gitterstruktur mit zentral kleinstem peripherwarts auf konzentrischen Zonen wachsendem hexagonalem Feldmittenabstand oder umgekehrt

Die Feldmittenabstande im poly bzw uberwiegend hexagonalen Hornhautepithel das als Einziges aus mehreren zuletzt 5–6 einander uberlagerten Flachenepithelien besteht betragen in der aussersten Epithelschicht 20–30 *µm*

2 Die invertierte Netzhaut als mogliche Beugungsgitter Rezeptoren Kombination (Einfach oder Doppelraster)

Histologische *Grundlagen*

Auch die Netzhaut des menschlichen Auges entsteht aus einem Flachenepithel aus der invaginierten vorderen Kugelkappe des neuralen Augenblaschens die zunachst nach demselben epithelialen Wachstumsmuster ausgebildet wird wie der aussere Teil der neuralen Augenbecherschicht der als spatere Pigment epithelschicht *auffallig regelmassige* hexagonale Zellgrenzstrukturen aufweist wie sie der Dichtestpackung prismatischer Zellen in nur einer *Zellage* entspre chen (M Schultze 1866 *Hogan* et al 1941) Durch appositionelles Wachstum am Netzhautaquator (Blechschmidt 1961) setzt sich das Netzhautflachenwachs tum – zu dem ein Dickenwachstum *hinzukommt* – *fort* Eine *Änderung* im epithelialen Wachstumsmuster ist weder an der Invaginationsgrenze der spa teren Ora serrata noch andernorts zu erkennen oder nachgewiesen Die fruheste Entwicklung in der invaginierten Retina besteht in der Ausbildung einer Glia architektonik die als Rohgerust Grobstruktur anzusehen ist (Mann 19_8 1949 Walter *akoarse skeleton* 1961 Uga & Smelser 1973) in der die Mullerschen Stutz oder Radialfasern durch ihre Senkrechtstellung zu den beiden Grenz *membranen der* Netzhaut ihre typische Formfestigkeit verleihen (Blechschmidt 196) Lebouvq (1903) vertrat die Meinung sowohl die membrana limitans externa als auch die Faserkorbe der Mullerschen *Zellen* seien als Reste der ursprunglichen interzellularen Zementsubstanz der fotalen Retina aufzufassen Cohen (1965) und Spitznas (19 0) belegten dass die aussere Grenz membran der Netzhaut – durch die im 7 embryonalen Entwicklungsmonat die Rezeptoren in den Spaltraum zwischen Netzhaut und Pigmentepithelschicht auswachsen, so dass ihnen die Netzhaut als sog invertierte Netzhaut lichtwarts unmittelbar vorgelagert ist – die Bezeichnung Membran deshalb nicht verdient weil die Zwischenraume im Zapfen Stabchen Verteilungsmuster in der Membran Ebene aus Lagen interzellularer zytoplasmatischer Verdichtungen bestehen (zonulae adhaerentes) deren Funktion primar mechanisch ist indem sie die Basis der Innenglieder der Rezeptoren mit den umgebenden Mullerstutzzellen sowie benachbarte Mullersche Stutzzellen untereinander verbinden (Spitznas 1970 s 44) H Muller der Entdecker der Gliastutzzellen hat fur die der in neren Grenzmembran nachstliegende Schicht der Netzhaut auf einen weiteren Tatbestand hingewiesen auf die wechselseitig sich bedingende Raumaufteilung d h Lage und Standortsverteilung zwischen Stutzfasern und Sehnervenbundeln die Radialfasern nehmen vorzugsweise die Lucken ein welche die plexusartig sich verbindenden Bundel der Sehnerven zwischen sich lassen (185? S ?0) Im Augenhintergrund wo starkere Nervenbundel von sehr verlangerten spalt formigen Lucken durchbrochen sind bilden die Radialfasern Langsreihen in

Fernbereich der mit Flachenepithelien belegten Hornhaut und Linse Im Fernbereich liefert ein hexagonales Beugungsgitter von einer kreispunktformigen Lichtquelle die in Fig 1 photographisch wiedergegebene Fraunhofersche Beugungsfigur sie enthalt ein zentrales kreispunktformiges achromatisches Beugungsscheibchen O Ordnung und in den Schnittpunkten dreier unter 60° kreuzenden Parallelenscharen (mit wellenlangenspezifischem Parallelenabstand) die chromatischen 1 und hoheren Beugungsordnungen der im Beleuchtungsspektrum vertretenen Wellenlangen in gitterformtypischer seitlicher Versetzung

Die O Beugungsordnung im Fraunhoferschen Beugungsbild eines einzelnen oder mehrerer – in makroskopischen Abstanden oder auch nur in nicht streng periodischer Ordnung – hintereinandergelagerter hexagonaler Beugungsgitter das sog zentrale Beugungsscheibchen ist nicht unahnlich dem Bildpunkt den eine Zonenplatte in periodischen Abstanden liefert bzw demjenigen zentralen Beugungsscheibchen mit dem die optische Theorie des menschlichen Auges in der Netzhautbildebene bei der Abbildung eines punktformigen Objektstrahlers zu rechnen gewohnt ist Seine Form und Grosse werden durch die Konstanten des optischen Systems und durch Beugung an der kreisformigen Pupille determiniert es weist eine kreisformige zentrale O Beugungsordnung auf die u a mit chromatischer Aberration behaftet ist und ringformig die O Ordnung umlagernde 1 und hohere Beugungsordnungen in denen die spektrale Auffacherung erfolgt

Eine Gitter Pupillenkombination im fokussierend abbildenden optischen System bringt in das zentrale Beugungsscheibchen in der Bildebene das sowohl bei geometrischoptischer wie gitteroptischer Betrachtung als fur die optische Punktabbildung und damit zugleich Bildubertragung allein ausschlaggebend betrachtet werden kann zumindest keine storenden Einflusse ein es vermag moglicherweise im Gegenteil den Betrag der chromatischen Aberration eher zu reduzieren Der Beitrag den als Beugungsgitter interpretierbare Flachenepithelien auf spharischen Grenzflächen von Linse und Hornhaut damit zur optischen Informationsubertragung in die Netzhautbildebene zu leisten vermogen kann somit in einem eher vorteilhaften Einfluss auf das Fraunhofersche Beugungsbild speziell auf dessen O Ordnung gesehen werden In ihr liegt die Fouriertransformierte die in allen Teilen koharente Amplituden und Phasenverteilung des Objektstrahlers vor

2. Die invertierte Netzhaut als mögliche Beugungsgitter-Rezeptoren-Kombination (Einfach- oder Doppelraster)

Histologische Grundlagen

Auch die Netzhaut des menschlichen Auges entsteht aus einem Flachenepithel aus der invaginierten vorderen Kugelkappe des neuralen Augenblaschens, die zunachst nach demselben epithelialen Wachstumsmuster ausgebildet wird wie der aussere Teil der neuralen Augenbecherschicht, der als spatere Pigmentepithelschicht auffallig regelmassige hexagonale Zellgrenzstrukturen aufweist, wie sie der Dichtestpackung prismatischer Zellen in nur einer Zellage entsprechen (M. Schultze 1866, Hogan et al. 1971). Durch appositionelles Wachstum am Netzhautaquator (Blechschmidt 1967) setzt sich das Netzhautflachenwachstum – zu dem ein Dickenwachstum hinzukommt – fort. Eine Änderung im epithelialen Wachstumsmuster ist weder an der Invaginationsgrenze, der spateren Ora serrata, noch andernorts zu erkennen oder nachgewiesen. Die fruheste Entwicklung in der invaginierten Retina besteht in der Ausbildung einer Gliaarchitektonik, die als Rohgerust, Grobstruktur anzusehen ist (Mann 1928, 1949, Wolter: skoarse skeleton, 1961, Uga & Smelser 1973), wobei die Mullerschen Stutz- oder Radialfasern durch ihre Senkrechtstellung zu den beiden Grenzmembranen der Netzhaut ihre typische Formfestigkeit verleihen (Blechschmidt 1961). Leboucq (1901) vertrat die Meinung, sowohl die membrana limitans externa als auch die Faserkorbe der Mullerschen Zellen seien als Reste der ursprunglichen interzellularen Zementsubstanz der fotalen Retina aufzufassen. Cohen (1965) und Spitznas (1970) belegten, dass die aussere Grenzmembran der Netzhaut – durch die im embryonalen Entwicklungsmonat die Rezeptoren in den Spaltraum zwischen Netzhaut und Pigmentepithelschicht auswachsen, so dass ihnen die Netzhaut als sog. invertierte Netzhaut lichtwarts unmittelbar vorgelagert ist – die Bezeichnung Membran deshalb nicht verdient, weil die Zwischenraume im Zapfen-Stabchen-Verteilungsmuster in der Membranebene aus Lagen interzellularer zytoplasmatischer Verdichtungen bestehen (zonulae adhaerentes), deren Funktion primar mechanisch ist, indem sie die Basis der Innenglieder der Rezeptoren mit den umgebenden Mullerstutzzellen sowie benachbarte Mullersche Stutzzellen untereinander verbinden (Spitznas 1970, s. 44). H. Muller, der Entdecker der Gliastutzzellen, hat fur die der inneren Grenzmembran nachstliegende Schicht der Netzhaut auf einen weiteren Tatbestand hingewiesen, auf die wechselseitig sich bedingende Raumaufteilung, d. h. Lage- und Standortverteilung zwischen Stutzfasern und Sehnervenbundeln: die Radialfasern nehmen vorzugsweise die Lucken ein, welche die plexusartig sich verbindenden Bundel der Sehnerven zwischen sich lassen (1857, S. 20). Im Augenhintergrund werden starkere Nervenbundel von sehr verlangerten spaltformigen Lucken durchbrochen und bilden die Radialfasern Langsreihen in

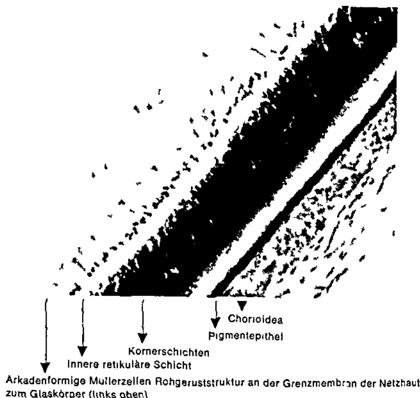


Fig 2
Netzhautquerschnitt mit arkadenformigem Glia Rohgerust in der inneren Netzhautschicht (Grenzschicht zum Glaskorper) (ca 6 embryonaler Entwicklungsmonat HL Farbung V – 570 x)

der Richtung des Nervenverlaufs (ebenda) Sie stehen im grossten Teil der Netzhaut senkrecht zur Limitans interna (S 69) und bilden Saulen welche durch Hohlraume getrennt sind wie Pfeiler eines Gewolbes Auf senkrechten *Schnitten entstehen zierliche Arkaden von betrachtlicher Hohe* (S 71) Die Radialfasern sind vermutungsweise als bindegewebelastischer Stutzapparat der Retina zu bezeichnen (S 73) Zur Makula hin werden sie allmahlich so fein dass sie schwer wahrnehmbar sind (S 70) Hogan et al (1971 S 489) betonen die in der inneren Grenz membran sich verastelnden Mullerzellfortsatze deckten polygonale Felder ab durch die der Glaskorper – den von Mullerfasern ab gesteckten Feldkonturen folgend – wellig durchhange Ein von diesen Autoren (Fig 9–71 S 483 1971) wiedergegebener elektronenmikroskopischer Quer schnitt illustriert die Art der beschriebenen Einlagerung von Sehnervenbundeln in die von Mullerfasern an der inneren Grenz membran ausgebildeten Arkaden zweifelsfrei Unsere eigenen lichtmikroskopischen Aufnahmen aus der inneren Grenzschicht der fotalen Netzhaut belegen die fruhe Ausbildung eines arkaden formigen Gliarohgerusts (Fig 2) mit im Flachschnitt polygonalen Feldstruktu

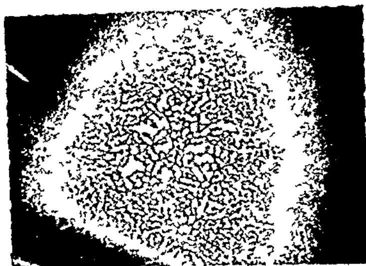


Fig 3
Netzhautfla hschnitt in der Grenzs hi ht der Netzhaut zum Glask rper Bildmitte *Polygonales Mullerzellen Gliarohgerust* (Schnitt et ca aquatorialer Vertikalmeridian d r Netzhaut emhr s naler Entwicklungsm onat V > 0 x IJE Farburg)

ren (Fig 3) das wir als plexusf rmiges Leitgerust fur den Sammel und Bun delungspr ess papillenwarts auswachsender Ganglienzellaxone interpretieren *Die Auffaltung des Glialeitgerusts mit Sehnervenbundeln schliesslich zeigt Fig 4 Es scheint ganz so als habe* das Gliagerust – wie in der ausseren Netzhaut *grenzschicht* fur die *Rezeptoren* auch in der inneren Grenzschicht eine me chanische Halterungsfunktion fur die Kabelstrange der Sehnerven zu erfullen M *glicherweise* besteht das Gliagerust der Netzhaut insgesamt aus Verdichtun gen interzellularer Sul stanzen an den Zellkanten primitiver Epithelzellen *Grenzflachen* sodass der vom Gliagerust umschlossene Raum fur Zell und *Nervenwand fur ken entlang bestimmten Leitlinien frei* ware Da die Sehnerven *bun lel Verlaufsfigur in der menschlichen Netzhaut oft* beschrieben wurde und z B bei H gan et al (U I Fig 10–8 *S 533) fur* das Gebiet um Makula und Papille abgebildet ist lasst sich durch eine *Modellskizze in Fig 5* illustrieren wie eine zu dieser komplementare aus *einer primitiven* Flachenepithel Zell grenzstruktur unmittelbar ableitbare *in vivo* – bei normalem Augeninnendruck

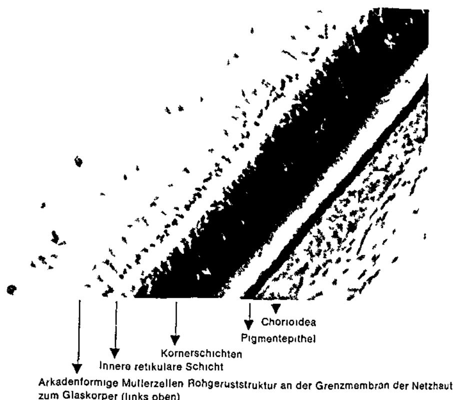


Fig 2

Netzhautquerschnitt mit arkadenformigem Glia Rohgerust in der inneren Netzhautschicht (Grenzschicht zum Glaskorper) (ca 6 embryonaler Entwicklungsmonat HE Farbung V = 370 x)

der Richtung des Nervenverlaufs (ebenda) Sie stehen im grossten Teil der Netzhaut senkrecht zur Limitans interna (S 69) und bilden Saulen, welche durch Hohlraume getrennt sind wie Pfeiler eines Gewolbes Auf senkrechten Schnitten entstehen zierliche Arkaden von betrachtlicher Hohe (S 71) Die Radialfasern sind vermutungsweise als bindegewebelastischer Stutzapparat der Retina zu bezeichnen (S 73) Zur Makula hin werden sie allmahlich so fein dass sie schwer wahrnehmbar sind (S 70) Hogan et al (1971 S 489) betonen die in der inneren Grenz membran sich verastelnden Mullerzellfortsatze deckten „polygonale Felder" ab durch die der Glaskorper – den von Mullerfasern abgesteckten Feldkonturen folgend – wellig durchhange Ein von diesen Autoren (Fig 9–71 S 483 1971) wiedergegebener elektronenmikroskopischer Querschnitt illustriert die Art der beschriebenen Einlagerung von Sehnervenbundeln in die von Mullerfasern an der inneren Grenzmembran ausgebildeten Arkaden zweifelsfrei Unsere eigenen lichtmikroskopischen Aufnahmen aus der inneren Grenzschicht der fotalen Netzhaut belegen die fruhe Ausbildung eines arkadenformigen Gliarohgerusts (Fig 2) mit im Flachschnitt polygonalen Feldstruktu

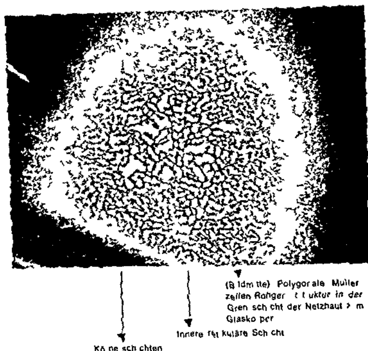


Fig 3
Netzhautflachschn tt in der Grenzschicht der Netzhaut zum Glaskorper Bildmitte Polygonales Mullerzellen Charohgerust (Schnittort ca aqual orialer Vertikalmeridian d r Netzha t 7 embryonaler Entwicklungsmonat V ~ 570 x HE Farbung)

ren (Fig 3) das wir als plexusformiges Leitgerust fur den Sammel und Bun delungsprozess papillenwarts auswachsender Ganglienzellaxone interpretieren Die Ausfullung des Glialeitgerusts mit Sehnervenbundeln schliesslich zeigt Fig 4 *Es scheint ganz so alt habe das Cliagerust – wie in der ausseren Netzhaut* grenzschicht fur die Rezeptoren – auch in der inneren *Gren schicht* eine me chanische Halterungsfunktion fur die Kabelstrange *der* Sehnerven *zu erfullen* Moglicherweise besteht das Gliagerust der *Netzhaut* insgesamt aus Verdichtun gen *interzellularer* Substanzen *an den Zellkanten* primitiver *Epithelzellen Grenzflachen sodass der vom Gliagerust umschlossene Raum fur Zell* und Axonwanderungen entlang bestimmten Leitlinien frei ware *Da* die Sehnerven bundel Verlaufsfigur in der menschlichen *Netzhaut oft beschrieben* wurde und z B bei Hogan et al (19/1 Fi 10–5 S 53t) *fur das Gebiet um* Makula und Papille abgebildet i t lasst sich dur h eine Modellskizze *ir F g 5* illustrieren wie eine zu dieser komplementare *aus einer primitiven* Flachenepithel Zell grenzstruktur *unmittelbar* ableitbare *m t z o – bei normalem* Augeninnendruck

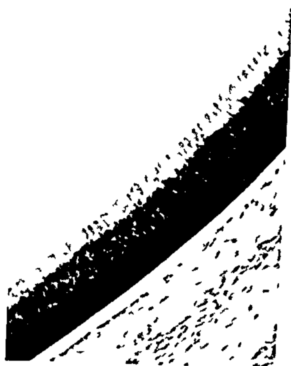


Fig 4
Netzhautquerschnitt Im Gliarohgerust der innersten Netzhautschicht eingelagerte Sehnervenbundel (64 mm Embryo HI Farbung V = 730 x)

– hexagonale Glialeit und gitterstruktur in der inneren Netzhautschicht anzusetzen ware Die Sehnervenbundel lagern sich einer hexagonalen Rasterleitstruktur sowohl in der peripheren Netzhaut mit ihrer zunachst radial zur Papille angelegten Bundelordnung ebenso zwanglos ein wie im Makulabereich in dem die makulopapillaren Sehnervenbundel eine eigenwillige mit der peripheren Bundelverlaufsfigur jedoch kompatible Sehnervenstrangordnung erzwingen

Fur eine gitteroptische Betrachtung der Gliarasterstruktur ergibt sich aus derselben Modellskizze (Fig 5 und 6) dass im Netzhautzentralgebiet auf zur Fovea konzentrischen nahezu kreisformigen in der Netzhautperipherie auf zu Fovea und Papille konzentrischen elliptischen Leitlinien masslich nahezu gleiche und von der Fovea aus peripherwarts wachsende Gitterkonstantenmasse zu erwarten waren die naherungsweise zugleich dem ortsspezifischen Sehnervenbundelabstand entsprachen Das innere Eingangs Raster (LR) der Netzhaut ware als Beugungsgitter zugleich ein Orts oder Raumfrequenzfilter in der Bildebene mit in der Fovea selbst maximaler zum Makularand hin auf kreisformigen Zonen abnehmender Ortsfrequenzcharakteristik Über sog Cassinische Kurven (Fig 6) die als geometrische Leitlinien zwischen zunachst zu einem Mono Pol

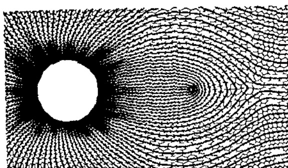


Fig 5

Hexagonale Rasterstruktur der Mullerschen Gliazellen *im zentralen Netzhautgebiet* (links Papille rechts Makula) mit eingelagerter Sehnervenbundel Verlaufsfigur Arbeitshypothetische Skizze

(Fovea) kon entrischen kreisformigen Zonen und danach zu einem Bipol (Fovea und Papille) konzentrischen elliptischen Netzhautzonen vermitteln lasst sich der Übergang zu peripheren Netzhautzonen darstellen in denen – der Radial form des Sehnervenbundelverlaufs entsprechend – *zunehmend geringere* Orts frequenzmasse zu erwarten sind Daten zur meridian und zonenspezifisch maxi malen Ortsfrequenzanalyse liegen in den Visuskurven und Isopterenlinien (Li nien gleicher exzentrischer Sehscharfe) vor Letztere folgen nahezu genau den beschriebenen Gesetzmassigkeiten der Konzentrizitat der Netzhautrasterzonen zum Foveapol und zum Fovea Papillen Bipol (Wertheim 1894) Eine nahe rungsweise Umrechnung der zonenspezifisch maximalen (photopischen) Visus werte in Netzhautstreckenmasse in einem facherformigen Segment der peri

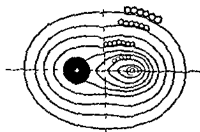


Fig 6

Linien in hexagonalen Gliaraster *des zentralen* Netzhautgebiets (links Papille rechts Makula) Randwarts sog Cassinische Kurven Linien gleicher hexagonaler Flachengrosse.

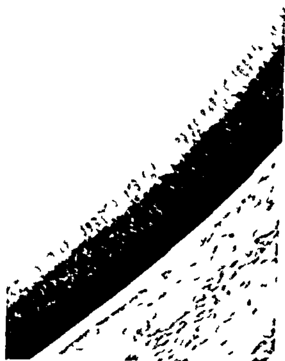


Fig 4

Netzhautquerschnitt Im Gliarohgerust der innersten Netzhautschicht eingelagerte Sehnervenbundel (64 mm Embryo HE Farbung V = 250 x)

– hexagonale Glialeit und gitterstruktur in der inneren Netzhautschicht anzusetzen ware Die Sehnervenbundel lagern sich einer hexagonalen Rasterleitstruktur sowohl in der peripheren Netzhaut mit ihrer zunachst radial zur Papille angelegten Bundelordnung ebenso zwanglos ein wie im Makulabereich in dem die makulopapillaren Sehnervenbundel eine eigenwillige mit der peripheren Bundelverlaufsfigur jedoch kompatible Sehnervenstrangordnung erzwingen

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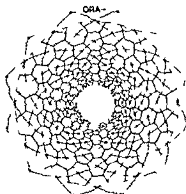


Fig 8
Modellskizze einer zum zentralen (Mono) Pol der Fovea zentrierten radialkonzentrischen hexagonalen Rasterstruktur *(photopisches Modell)* (hyperbolische Spiralen als geometrische Leitlinien) Nicht *masstabgerecht*

chende Gitterkonstantenmasse und im Ausgangsraster AR (aussere Grenzmembran) *die durch Polyak Osterberg u a* bekannten *ortsspezifischen Zapfenabstandsmasse* anzusetzen so ist das Netshautgliagerust gitteroptisch als Doppelraster zu behandeln (mit in der Fovea bestenfalls identischen, peripherwarts zunehmend *differierenden Gitterkonstantenmassen* lt Fig 10) Lasst sich hingegen – trotz der angefuhrten im Einzelnen aber noch ungenugend prazisierten

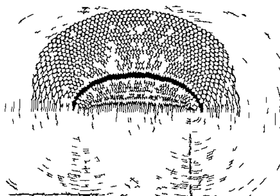


Fig 9
M d ll k z e e ner zum z ntralen (Bi) Pol v n Fovea und Papille zentrierten rad al k nz ntrisch n hexag nalen Rasterstruktur *(sk topisches Modell)* (Hyperbeln als geo met sche L l n en) *Geschwarzte Zone* = Zone des scharfsten skotopischen Sehens mit grosster Stabchendichte Nicht masstabgerecht

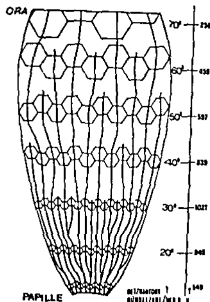


Fig [illegible]
Bundelungsprinzip der Sehnerven im facherformigen Netzhautsegment der peripheren Netzhaut und Wachstumsfunktion der Gitterkonstante im hexagonalen Raster Rechts Sehnervenbundelzahl pro vertikalem Netzhautmeridian bei Zugrundelegung der in Netzhautstreckenmasse umgerechneten photopischen Visuswerte als Gitterkonstantenmassen

pheren Netzhaut fuhrt z B zu einem in Fig 7 illustrierten Raster und Sehnervenbundelungsprinzip das der histologischen Definition einer plexusformigen Leitstruktur fur die Sehnervenbundelung ebenso genugt wie der geometrischen einer radialkonzentrischen hexagonalen Rasterstruktur Die auf einer vertikalen Meridianzone der Netzhaut zu erwartende maximale Sehnervenbundelzahl ware lt Fig 7 bei 30 mit ca 1021 Bundeln zu erwarten einer von Deyl (1895) im Optikus ermittelten Gesamtbundelzahl (800–1200 Bundel) Zwischen einer vertikalen Netzhautzone bei 30 und der Papille wurden die Sehnervenbundel zunehmend in der Netzhauttiefe gestaffelt worauf sowohl Abbildungen wie Beschreibungen verschiedener Autoren als auch die Daten zur Netzhautdicke hinweisen Fig 8 wurde sich als stark vergrossernde Skizze des ER in der Fovea Fig 9 als Skizze fur skotopisches Sehen anbieten

Gitteroptisches Modell

Haben wir in der inneren und ausseren Netzhautgrenzmembran mit einer radialkonzentrischen hexagonalen Gitterstruktur zu rechnen und fur das – im Vergleich zum skotopischen Sehen mit der optimaleren Ortsfrequenz ausgezeichnete – photopische Sehen im I R den photopischen Visuswerten entspre

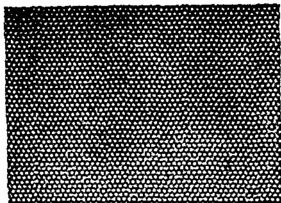


Fig 11
Verteilungsmuster der Interferenzmaxima in der 1 Fresnelebene eines hexagonalen Amplitudengitters mit g = 20 µm und sehr weitgehend ausgebleichten Gitterstegen (z = g²/2 66 λ) (V = ca 160 x)

bereich hinter Transmissions Flachengittern erfolgt in jeder der Fresnel und Fourierebenen die Lichtmodulation auf einer Tiefenstrecke in z Richtung Beim hexagonalen Amplitudengitter liegt das 1 Fourierbild des Gitters bei senkrechter Beleuchtung mit parallelem koharentem Licht in einer durch z = 1 5 g²/λ bestimmten Ebene hinter dem Gitter (g = Gitterkonstante/λ = Wellenlange) (Bei einem Phasengitter verkurzt sich der z Abstand der Fourier wie der zwischen Gitter und 1 Fourierebene liegenden Fresnelschen Interferenzebenen um einen aus der Phasenbedingung ableitbaren Betrag Ebenso verkurzt sich der z Abstand bei leicht konvergenter Gitterbeleuchtung um eine hier vernachlassigbare Strecke) In Fig 11 geben wir das Verteilungsmuster der Interferenzmaxima in der gitternachsten Fresnelebene eines hexagonalen Amplitudengitters mit g = 20 µm und weitgehend ausgebleichten d h absorptionsfreien Gitterstegen wieder Diese z Ebene folgt der Beziehung z = g²/2 66 λ 0 375 g²/λ der z Wert stellt somit einen Viertelbetrag der z Strecke fur die 1 Fourierebene dar Das Interferenzbild in dieser Fresnelebene weist in der Richtung jeder der 3 unter 60° kreuzenden Flachenkoordinaten eine Verdopplung der Periodik in der Gitterebene auf d h hinter allen Schnittpunkten der durch die Gitterstege gelegten 3 Koordinaten liegen diskrete Interferenzmaxima vor Auch in allen weiteren Fresnelebenen sind diskrete Interferenzmaxima in den Schnittpunkten dreier unter 60° kreuzenden Parallelenscharen zu finden lediglich die Periodenverdopplung fehlt in einer bestimmten z Ebene (Fig 12) Aufgrund der umgekehrt proportionalen Beziehung *zwischen z und λ* liegen in jeder Fresnelebene die Interferenzmaxima der im Beleuchtungsspektrum besetzten Wellenlangen in frequenzproportionaler bzw monochromatischer Tiefenstaffe

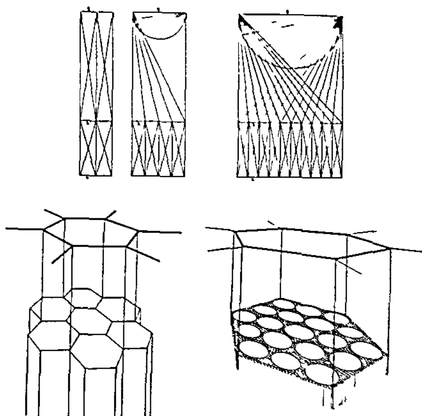


Fig 10
Modellskizzen fur eine hexagonale Doppelraster – Rezeptorenkombination in der Netzhaut mit zentral bestenfalls identischer peripherwarts zunehmend differierender Gitterkonstantenperiode im Eingangs bzw Ausgangsraster Die Gitterperiodik im Ausgangsraster wird durch das Verteilungsmuster der Rezeptoren bestimmt deren Aussenglieder sich in z Richtung hinter dem Ausgangsraster erstrecken

Belege – eine entsprechende Gliarasterstruktur in der inneren Netzhautgrenz schicht nicht definitiv nachweisen so ist lediglich das AR als Einzelraster zu behandeln Im Nahbereich des Einzel – oder Doppelrasters sind die Rezeptoren eingelagert Ihre photorezeptiven Aussenglieder besitzen eine ortsspezifische Länge und sind am zentralen Netzhautort senkrecht zum AR orientiert peri pherwarts scheint ihre Langsachse in Richtung auf die Pupillenmitte zu weisen Derart definierte wechselseitige Lage und Orientierungsbeziehungen entspra chen streng den durch eine Gitter Rezeptoren Kombination in der Netzhaut ebene zu erfullenden Bedingungen Die Rolle eines Doppel oder Einfachrasters ware in der beugungsoptischen Lichtmodulation aus der Bildebene (ER oder AR Ebene) auf die Rezeptorenaussenglieder zu sehen in der Abbildung des Fraunhoferschen Beugungsbilds auf als wave guides (Snyder & Menzel 1975) interpretierbare Photorezeptoren Im Interferenzebenen Raumgitter im Nah

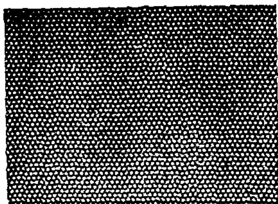


Fig. 11
Verteilungsmuster der Interferenzmaxima in der 1. Fresnelebene eines hexagonalen Amplitudengitters mit g = 90 µm und sehr weitgehend ausgebleichten Gitterstegen ($z = g^2/0{,}66\,\lambda$) (V = ca. 160 x)

bereich hinter Transmissions-Flächengittern erfolgt in jeder der Fresnel- und Fourierebenen die Lichtmodulation auf einer Tiefenstrecke in z-Richtung. Beim hexagonalen Amplitudengitter liegt das 1. Fourierbild des Gitters bei senkrechter Beleuchtung mit parallelem kohärentem Licht in einer durch $z = 1{,}5\,g^2/\lambda$ bestimmten Ebene hinter dem Gitter (g = Gitterkonstante, λ = Wellenlänge). (Bei einem Phasengitter verkürzt sich der z-Abstand der Fourier- wie der zwischen Gitter und 1. Fourierebene liegenden Fresnelschen Interferenzebenen um einen aus der Phasenbedingung ableitbaren Betrag. Ebenso verkürzt sich der z-Abstand bei leicht konvergenter Gitterbeleuchtung um eine hier vernachlässigbare Strecke.) In Fig. 11 geben wir das Verteilungsmuster der Interferenzmaxima in der gitternachsten Fresnelebene eines hexagonalen Amplitudengitters mit g = 90 µm und weitgehend ausgebleichten, d. h. absorptionsfreien Gitterstegen wieder. Diese z-Ebene folgt der Beziehung $z = g^2/2{,}66\,\lambda = 0{,}375\,g^2/\lambda$; der z-Wert stellt somit einen Viertelbetrag der z-Strecke für die 1. Fourierebene dar. Das Interferenzbild in dieser Fresnelebene weist in der Richtung jeder der 3 unter 60° kreuzenden Flächenkoordinaten eine Verdopplung der Periodik in der Gitterebene auf, d. h. hinter allen Schnittpunkten der durch die Gitterstege gelegten 3 Koordinaten liegen diskrete Interferenzmaxima vor. Auch in allen weiteren Fresnelebenen sind diskrete Interferenzmaxima in den Schnittpunkten dreier unter 60° kreuzenden Parallelenscharen zu finden, lediglich die Periodenverdopplung fehlt in einer bestimmten z-Ebene (Fig. 12). Aufgrund der umgekehrt proportionalen Beziehung zwischen z und λ liegen in jeder Fresnelebene die Interferenzmaxima der im Beleuchtungsspektrum besetzten Wellenlängen in frequenzproportionaler bzw. monochromatischer Tiefenstaffe-

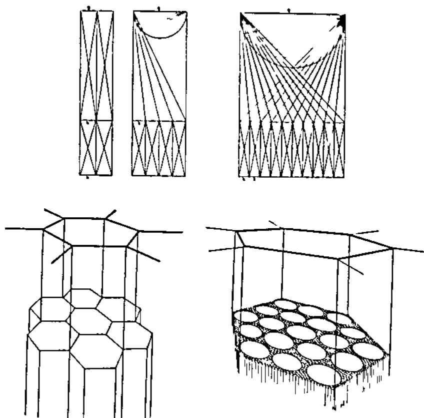


Fig 10

Modellskizzen fur eine hexagonale Doppelraster – Rezeptorenkombination in der Netzhaut mit zentral bestenfalls identischer peripherwarts zunehmend differierender Gitterkonstantenperiode im Eingangs bzw Ausgangsraster Die Gitterperiodik im Ausgangsraster wird durch das Verteilungsmuster der Rezeptoren bestimmt deren Aussenglieder sich in z Richtung hinter dem Ausgangsraster erstrecken

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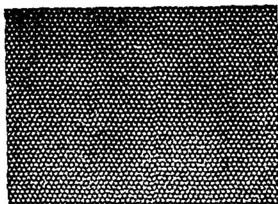


Fig. 11

Verteilungsmuster der Interferenzmaxima in der 1. Fresnelebene eines hexagonalen Amplitudengitters mit g = 20 µm und sehr weitgehend ausgebleichten Gitterstegen ($z = g^2/2{,}66\,\lambda$) (V = ca. 160 x)

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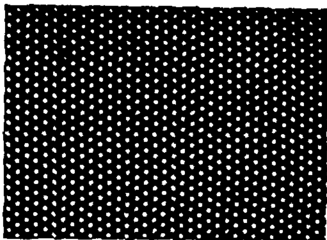


Fig 19

Verteilungsmuster der *Interferenzmaxima in der letzten Fresnelebene (z = g²/0,5 λ)* vor dem 1 Fourierbild des Gitters Hexagonales Amplitudengitter mit sehr weitgehend ausgebleichten Gitterstegen g = 20 μm V = ca 160 x)

lung hintereinander in z Richtung In der gitternächsten Fresnelebene belegt das Frequenzband für λ = 430–780 nm bei g= 20 μm eine z Tiefenstrecke von 157 μm wobei λ = 430 nm am gitterfernen Ende bei z = 349 μm λ = 780 nm am gitternahen Ende bei z = 192 μm liegt λ = 555 nm als Symmetrie Wellen lange in der Mitte zwischen den gewählten Grenzwellenlangen im sichtbaren Spektrum bei z = 270 μm Belegen die Zapfenaussenglieder hinter einem Einzel oder Doppelraster diese z Tiefenstrecke so wird ihnen ein der Amplituden oder Frequenzmodulation zugängliches spektrales Signalband einer Oktav an geboten aus dem sie ihrer trichromatischen photochemischen Spektralempfind *lichkeit entsprechend die für sie relevante Information auszufiltern* in der Lage sein konnten

Entspricht aber nun auch das Verteilungsmuster der Zapfen zumindest im farbtüchtigsten Teil der Netzhaut (Makula und nahe Peripherie) dem Vertei lungsmuster der Interferenzmaxima in Fresnelebenen hinter hexagonalen Git tern? Polyak (1968) hat belegt dass in der menschlichen Fovea das Prinzip der Dichtestpackung von Zapfen gilt in dem die Zapfenstandorte als die Schnittpunkte dreier unter 60° kreuzenden Parallelenscharen definiert sind M Schultze (1866) hat an frischen menschlichen Netzhauten gezeigt dass bis zur peripheren Netzhaut hin das Zapfenverteilungsmuster demselben Standort verteilungsprinzip entspricht (die Zapfenstandorte sind als die Schnittpunkte hyperbolischer Spiralen und konzentrischer Kreise definiert) Zapfen in noch periphereren Netzhautzonen sind kaum noch als voll farbtüchtig zu betrachten Gilt aber dieses Zapfenverteilungsprinzip zumindest in zentralen Netzhautge bieten so kann wiederum für eine gitteroptische Erklärung der Netzhaut nur

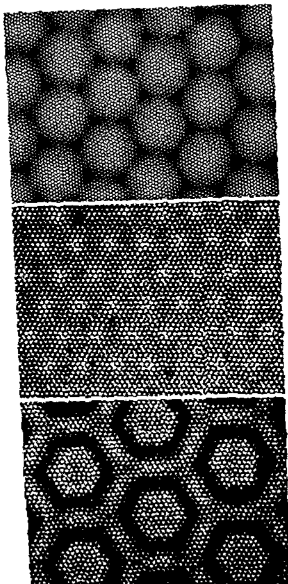


Fig 13

Verteilungsmuster der Interferenzmaxima in der 1 Fresnelebene des Ausgangsrasters bei hexagonaler Amplituden Doppelrastern

Ob   Gitterkonstante g im Eingangsraster ER = 29 μm im Ausgangsraster AR ~ 90 μm Winkelversetzung zwischen AR und ER ca 3 Grad (Moirefigur) (V 13 x)

Mitte   g im ER ?/m im AR 0/m (V 150 x)

Unten   g im ER 90/m im AR m (V 150 x)
(Die dunklen Sechsecke stellen keine Moirefigur sondern eine Beugungserscheinung an den Kanten des ER dar)

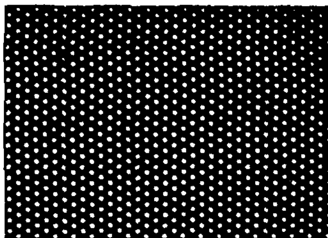


Fig 12
Verteilungsmuster der Interferenzmaxima in der letzten Fresnelebene ($z = g$ 0,82 λ) vor dem 1. Fourierbild des Gitters. Hexagonales Amplitudengitter mit sehr weitgehend ausgebleichten Gitterstegen $g = 20$ µm V = ca. 160 x)

lung hintereinander in z-Richtung. In der gitternächsten Fresnelebene belegt das Frequenzband für λ = 430–780 nm bei g = 20 µm eine z-Tiefenstrecke von 157 µm, wobei λ = 430 nm am gitterfernen Ende bei z = 349 µm, λ = 780 nm am gitternahen Ende bei z = 192 µm liegt. λ = 555 nm als Symmetrie-Wellenlänge in der Mitte zwischen den gewählten Grenzwellenlängen im sichtbaren Spektrum bei z = 270 µm. Belegen die Zapfenaussenglieder hinter einem Einzel- oder Doppelraster diese z-Tiefenstrecke, so wird ihnen ein der Amplituden- oder Frequenzmodulation zugängliches spektrales Signalband einer Oktav angeboten, aus dem sie ihrer trichromatischen photochemischen Spektralempfindlichkeit entsprechend die für sie relevante Information auszufiltern in der Lage sein könnten.

Entspricht aber nun auch das Verteilungsmuster der Zapfen zumindest im farbtüchtigsten Teil der Netzhaut (Makula und nahe Peripherie) dem Verteilungsmuster der *Interferenzmaxima in Fresnelebenen* hinter hexagonalen Gittern? Polyak (1968) hat belegt, dass in der menschlichen Fovea das Prinzip der Dichtestpackung von Zapfen gilt, in dem die Zapfenstandorte als die Schnittpunkte dreier unter 60° kreuzenden Parallelenscharen definiert sind. M. Schultze (1866) hat an frischen menschlichen Netzhauten gezeigt, dass bis zur peripheren Netzhaut hin das Zapfenverteilungsmuster demselben Standortverteilungsprinzip entspricht (die Zapfenstandorte sind als die Schnittpunkte hyperbolischer Spiralen und konzentrischer Kreise definiert). Zapfen in noch periphereren Netzhautzonen sind kaum noch als voll farbtüchtig zu betrachten. Gilt aber dieses Zapfenverteilungsprinzip zumindest in zentralen Netzhautgebieten, so kann wiederum für eine gitteroptische Erklärung der Netzhaut nur

Wert ?gcos30 /3 hat gilt tg α 0 5//3 g/z = x/z und sin α = 1 54 λ/g (in den Grenzen eines Messfehlers fur die 1 Fresnelebene ca 1 5 λ/g) Die Beziehung z = g /2 66 λ lautet unter Aufnahme von x damit z = g x/1 54λ Gehen wir nun vom zentralsten Netzhautort (0) von x = 2gcos30°/3 aus und setzen peripher warts x als ortsspezifisch bekannten Wert ein so lasst sich z als Variable be rech en Wir konnen aber auch bei 0 auf die Verarbeitung der uber die Pe riodenverdopplung in der 1 Fresnelebene zustandekommenden sekundaren (ge radzahligen) Maxima verzichten und von g = x ausgehen unser 1 Formelglied lautet dann z = g x/2 66 λ (bei x = g) das 2 Formelglied entsprechend z = x² ? 66 λ (Ein λ/4 Phaseneffekt wurde z um 1/4 ein λ/2 Phaseneffekt um 1/2 reduzieren) Die Relation von g x muss sich dabei peripherwarts von 0 nicht sprunghaft von Meridian zu Meridianzone andern also jeweils einer strengen Beziehung von g = k x/cos30 mit k = 1 5 3 4 5 6 folgen sondern kann sich durchaus kontinuierlich andern.

Lediglich uber das 1 Formelglied bzw uber die Summe beider Glieder (Dop pelrastermodell) lasst sich eine mogliche Beziehung zur anatomischen Netzhaut dicke herstellen Über das 2 Glied erhalten wir die in beiden Modellansatzen zwischen der ausseren Grenzmembran (AR) und den Rezeptorenaus engliedern in gleicher Weise gultigen Beziehungen Als Gitterkonstante im ER (g) wahlen wir die dem photopischen Visuswert entsprechende Netzhautmasstrecke (Sp 4 in Tab 1) als Gitterkonstante x im AR das ortsspezifische Zapfenabstandsmass (Sp 5) Eine Brechungsindexdifferenz zwischen Glaskorper und Netzhaut ver nachlassigen wir Die im photopischen Sehen maximal zu modulierende Wel lenlange ist λ = 555 nm Die Winkelneigung vertikaler Meridiane zu einfallen den Lichtkegeln berucksichtigen wir durch einen naherungsweise mit cos³ ψ ermittelten Korrekturfaktor wobei ψ den Neigungswinkel einfallender Licht kegel zur primaren Augenachse darstellt deren hinterer Pol zwi chen Papille und Fovea liegt Die theoretische funktionelle Netzhautdicke F ergibt sich aus der Summe von f dem Dickenmass zwischen ER und AR fur λ_{max} 555 nm und f dem Abstand zwischen AR und z Ebene am Zapfenaussenglied (Sp 9 (in Tab 1)

$$F \quad f \quad f \quad \frac{g\,x\cos^3\psi}{2\,66\,\lambda} + \frac{x^2\cos^3\psi}{2\,66\,\lambda}$$

Da f jedoch lediglich eine mehr oder weniger grosse Teilstrecke des ortsspe zifischen Langenmasses der Rezeptoren (Sp 10 in Tab 1) darstellen muss er rechnen wir in Sp 11 die funktionelle Netzhautdicke F' *uber die Summe von Sp 9 10* die z T einen grosseren mindestens jedoch gleichen Betrag als die Summe n Sp 6 9 ergibt

eine hexagonale Gitterform in Frage kommen die *allein ein* geometrisch ent sprechend geordnetes Interferenzmuster *liefert* *Fig 13* gibt das Verteilungs muster der Interferenzmaxima in einer Fresnelebene *hinter* Transmissions Dop pelrastern wieder die aus 2 *hintereinandergelagerten hexagonalen* Amplituden gittern bestehen Auch hier folgt das Interferenzmuster denselben geometrischen Gesetzen *wie hinter einem* einzigen Gitter Bei einer Winkelversetzung der Gitterkoordinaten zueinander tritt erwartungsgemass ein Moirebild auf

Gitteroptische Modellrechnung zur Netzhaut

Eine gitteroptische Modellrechnung zur Netzhaut (Tab 1) *lasst sich als Einfach* und Doppelraster Näherungsrechnung *z B* *fur* den temporalen Teil des hori zontalen Netzhautmeridians *durchfuhren* Über die Doppelrasterrechnung kann eine theoretische funktionelle Netzhautdickenkurve (*in vivo* Netzhautdicke) *ermittelt* und mit den im anatomischen *Zustand* gemessenen Daten zur Netz hautdicke *verglichen werden* Als Modulations *ebene in z Richtung hinter* dem Einfach oder *Doppelraster wahlen* wir die gitternächste Fresnelebene (z 0 375 g ²/λ) *Dies* insbesondre auch deshalb weil entsprechende Versuche zeigen dass bei *in den* Gitterstegen sehr weitgehend ausgebleichten d h nahezu ebenso wie *in den* Gitterlucken absorptionsfreien Amplitudengittern (und besonders *auch bei λ/4 Phasengittern) beim Doppelraster nicht – wie Lau an Amplituden* Linienrastern mit vollig absorbierendem Steg *zeigte* (1948) – nur eine einzige *Wellenlänge ausgefiltert* d h in einer bestimmten Fresnelebene moduliert wird *sondern lediglich* eine Symmetrie Wellenlänge im Spektrum maximal und Wellenlängen bei λ_{max} ± 25 % noch zu ca 40–60 % mitmoduliert werden Die ± *25 % Bedingung wurde bei* λ_{max} = *555* nm *z B* *fur 416 nm und 740 nm* gelten Eine nach dem Modulationsgrad in Abhangigkeit von der Wellenlange *aufgetragene* Kurve wurde dem Gaussschen Kurvenbild der spektralen Emp *findlichkeitssummen* oder einzelkurve der Zapfen gleichen die eher noch bedeutend steiler zu den Randwellenlangen des Spektrums hin abfallt

Wie *lasst* sich nun das Gitterkonstantenmass *im AR in die Formel fur die* gitternachste Fresnelebene des ER *einbringen?* Fig 13 belegt dass wir bei einer Gitterkonstantendifferenz zwischen ER und AR bei richtig gewahltem z Wert *jeweils* in den Gitterlucken des AR Helligkeitsmaxima erhalten Lau (1948) leitete fur das Amplituden Liniendoppelraster die fur die 1 Fresnelebene gul tige Beziehung z = g ²/2 λ aus sin α = 2 λ g *und* tg α = g/z ab (bei kleinem α sin ≃ tg) In der Mitte zwischen 2 um den Betrag g im AR auseinanderliegen den Maxima *lag jeweils* ein weiteres Maximum Bezeichnen wir den Abstand der Maxima im AR mit x so gilt zugleich sin α λ/g und tg α = g/2z d h z = g x/λ wobei x = g/2 Entsprechend lasst sich die 1 Fresnelebenenbedingung fur das hexagonale Gitter *umschreiben* da x (Zapfenabstandsmass im AR) den

Wert ?gcos30°/3 hat gilt tg α = 0 5//35 g/z = x/z und sin α = 1 54 λ/g (in den Grenzen eines Messfehlers fur die 1 Fresnelebene ca 1 5 λ/g) Die Beziehung z - g /2 66 λ lautet unter Aufnahme von x damit z = g x/1.54λ Gehen wir nun vom zentralsten Netzhautort (0) von x = 2gcos30 /3 aus und setzen peripher warts x als ortsspezifisch bekannten Wert ein so lasst sich z als Variable be rechnen Wir konnen aber auch bei 0° auf die Verarbeitung der uber die Pe riodenverdopplung in der 1 Fresnelebene zustandekommenden sekundaren (ge radzahligen) Maxima verzichten und von g = x ausgehen unser 1 Formelglied lautet dann z = g x/2 66 λ (bei x = g) das 2 Formelglied entsprechend z = x^2/2 66 λ (Ein λ/4 Phaseneffekt wurde z um 1/4 ein λ/2 Phaseneffekt um 1/2 reduzieren) Die Relation von g x muss sich dabei peripherwarts von 0 nicht prunghaft von Meridian zu Meridianzone andern also jeweils einer strengen Beziehung von g = k x/cos30 mit k = 1 5 3 4 5 6 folgen sondern kann sich durchaus kontinuierlich andern.

Lediglich uber das 1 Formelglied bzw uber die Summe beider Glieder (Dop pelrastermodell) lasst sich eine mogliche Beziehung zur anatomischen Netzhaut dicke herstellen Über das 2 Glied erhalten wir die in beiden Modellansatzen zwischen der ausseren Grenz membran (AR) und den Rezeptorenaussengliedern in gleicher Weise gultigen Beziehungen Als Gitterkonstante im ER (g) wahlen wir die dem photopischen Visuswert entsprechende Netzhautmasstrecke (Sp 4 in Tab 1) als Gitterkonstante x im AR das ortsspezifische Zapfenabstandsmass (Sp 5) Eine Brechungsindexdifferenz zwischen Glaskorper und Netzhaut ver nachlassigen wir Die im photopischen Sehen maximal zu modulierende Wel lenlange ist λ = 555 nm Die Winkelneigung vertikaler Meridiane zu einfallen den Lichtkegeln berucksichtigen wir durch einen naherungsweise mit $\cos^3 \psi$ ermittelten Korrekturfaktor wobei ψ den Neigungswinkel einfallender Licht kegel zur primaren Augenachse darstellt deren hinterer Pol zwischen Papille und Fovea liegt Die theoretische funktionelle Netzhautdicke F ergibt sich aus der Summe von f dem Dickenmass zwischen ER und AR fur λ_m 555 nm und f dem Abstand zwischen AR und z Ebene am Zapfenaussenglied (Sp 9 (in Tab 1)

$$F \quad f \quad f \quad \frac{g\,x\,\cos^3\psi}{2\,66\,\lambda} + \frac{x^2\cos^3\psi}{2\,66\,\lambda}$$

Da f jedoch lediglich eine mehr oder weniger grosse Teilstrecke des ortsspe zifischen Langenmasses der Rezeptoren (Sp 10 in Tab 1) darstellen muss er rechnen wir in Sp 11 die funktionelle Netzhautdicke F' uber die Summe von Sp) + 10 die z T einen grosseren mindestens jedoch gleichen Betrag als die Summe v n Sp (+ 9 ergibt

Ergebnis der Modellrechnung

Die Fig 14–16 stellen photographische Aufnahmen in der Bildebene (Fig 14) bzw in der Fresnelebene je eines in der Fokusebene eines Objektivs eingelagerten hexagonalen Einfach und Doppelrasters (Fig 15/16) dar und sollen die beschriebene und der Modellrechnung zugrundegelegte *Bildmodulation* illustrieren

Einfachraster (AR)

Haben wir lediglich die gitteroptische Wirkung eines einzigen Beugungsrasters in der äusseren Netzhaut*membran* zu berucksichtigen so liefern die Sp 6 und 7 der Tab I die Daten zur ortsspezifischen Tiefenlage der frequenzproportional in z Richtung gestaffelten *diskreten* Interferenzmaxima fur 2 Grenzwellenlangen des sichtbaren Spektrums (0 43 und 0 78 μm) Sp 8 die Gesamtlange des in der gitternachsten Fresnelebene den Zapfenaussengliedern angebotenen Frequenzbandes In diesem Frequenzband ware – bei Fehlen eines LR – der interferenzoptische Modulationsgrad fur alle Wellenlangen gleichgross (dies widerspricht dem Kurvenverlauf der Zapfen Spektralempfindlichkeit) In Netzhautgebieten ausserhalb des stabchenfreien Zentralgebiets (ϕ ca 100 μm) in denen bis zur Ringzone des scharfsten skotopischen Sehens (bei ca 20° Neigung zur Augenachse) zunehmend mehr Stabchen (ca 25 1 Zapfen) orawarts wieder weniger Stäbchen (ca 10 1) in die Zwischenraume zwischen Zapfen eintreten ware die Frage zu klären ob ein unsrer Modellrechnung entsprechendes beugungsoptisches Zusammenwirken der von Zapfen im AR belegten Gittersteg und Luckenflachen auch dort moglich bleibt Erste Versuche mit Gittern die z B das Zapfen Stabchen Verteilungsmuster in bestimmten Netzhautgebieten kopieren scheinen eine positive Antwort nahezulegen (das AR ware gleichsam als flächige Ineinanderlagerung zweier Gitter mit unterschiedlichen Gitterkonstanten und entsprechend unterschiedlicher optischer Wirkung zu betrachten)

Fig 14

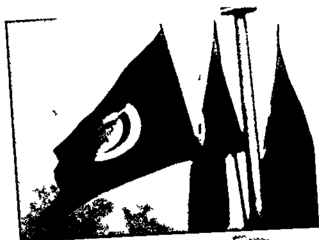
Fokusebene eines 50 mm Photoobjektivs (Blende 16) ohne Bildmodulation an einem Gitter Vorlage fur Fig 15/16 Mikrophot Aufn V = 63 x

Fig 15

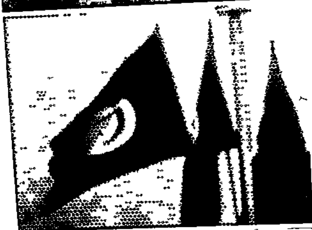
Bildmodulation in der 1 Fresnelebene eines in die Fokusebene des Photoobjektivs (f 50 mm Blende 16) eingelagerten hexagonalen Gitters (g = 20 μm in den Stegen weitgehend ausgebleichtes Amplitudengitter) Mikrophot Aufn V = 63 x

Fig 16

Bildmodulation in der 1 Fresnelebene des Ausgangsrasters bei einem in die Fokusebene des 50 mm Photoobjektivs (Blende 16) eingelagerten hexagonalen Doppelraster (LR g 72 μm AR g 20 μm in den Stegen weitgehend ausgebleichte Amplitudengitter) Mikrophot Aufn V = 63 x



14



15



16

Ergebnis der Modellrechnung

Die Fig 14–16 stellen photographische Aufnahmen in der Bildebene (Fig 14) bzw in der 1 Fresnelebene je eines in der Fokusebene eines *Objektivs* eingelagerten *hexagonalen* Einfach und Doppelrasters (Fig 15/16) dar und sollen *die beschriebene* und der *Modellrechnung* zugrundegelegte Bildmodulation illustrieren

Einfachraster (AR)

Haben wir lediglich die gitteroptische Wirkung eines einzigen *Beugungsrasters in der ausseren* Netzhaut membran zu berucksichtigen so liefern die Sp 6 und 7 *der Tab 1* die *Daten* zur ortsspezifischen Tiefenlage der frequenzproportional in z Richtung gestaffelten diskreten Interferenzmaxima für 2 Grenzwellenlangen des sichtbaren Spektrums (0 43 und 0 78 μm) Sp 8 die Gesamtlange des in der gitternachsten Fresnelebene den Zapfenaussengliedern angebotenen Frequenzbandes In diesem Frequenzband ware – bei Fehlen eines FR – der interferenzoptische Modulationsgrad fur alle Wellenlangen gleichgross (*dies* widerspricht dem Kurvenverlauf der Zapfen Spektralempfindlichkeit) In Netzhautgebieten ausserhalb des stabchenfreien Zentralgebiets (Ø ca 100 μm) in *denen bis zur Ringzone* des schärfsten skotopischen Sehens (*bei ca* 20° Neigung zur Augenachse) zunehmend mehr Stabchen (ca 25 1 *Zapfen*) orawärts wieder weniger Stabchen (ca 10 1) in die Zwischenraume zwischen Zapfen eintreten ware die Frage zu klaren ob ein unsrer Modellrechnung entsprechendes beugungsoptisches Zusammenwirken der von Zapfen im AR belegten Gittersteg und Lückenflächen auch dort möglich bleibt Erste Versuche mit Gittern die z B das Zapfen Stabchen Verteilungsmuster in bestimmten Netzhautgebieten kopieren scheinen eine positive Antwort nahezulegen (das AR ware *gleichsam als flachige Ineinanderlagerung* zweier Gitter mit unterschiedlichen Gitterkonstanten und entsprechend *unterschiedlicher optischer Wirkung* zu betrachten)

Fig 14

Fokusebene eines 50 mm Photoobjektivs (Blende 16) ohne Bildmodulation an einem Gitter Vorlage fur Fig 15/16 Mikrophot Aufn V = 63 x

Fig 15

Bildmodulation in der 1 Fresnelebene eines in die Fokusebene des Photoobjektivs (f 50 mm *Blende* 16) eingelagerten *hexagonalen* Gitters (g = 20 μm *in den* Stegen weitgehend ausgebleichtes Amplitudengitter) Mikrophot Aufn V = 63 x

Fig 16

Bildmodulation in der 1 Fresnelebene des Ausgangsrasters bei einem in die Fokusebene des 50 mm Photoobjektivs (Blende 16) eingelagerten hexagonalen Doppelraster (LK g 12 μm AR g = 20 μm in den Stegen weitgehend *ausgebleichte* Amplitudengitter) Mikrophot Aufn V 63 x

unter max 0 / µm Lange kann also vergleichsweise zur Frequenzbandbreite fur Zapfen hochstens zu einer summarischen Helligkeitsanalyse nicht zu einer Spektralanalyse ausreichen

Um in jeder Netzhautzone auch das kurzwellige Spektralende *hinter dem AR* (f in Sp 6) empfangen zu konnen muss eine zonenspezifische funktionelle mechanische Zapfenlange zur Verfugung stehen die wir mit Naherungsdaten in Sp 10 angeset t haben Gegenuber den im anatomischen Zustand gemesse nen Daten (Polyak u a) ergeben sich hochstens zwischen 5° und 30° bedeuten dere Unterschiede wobei unsre Werte grosser sind Bereits W J Schmidt (1934) hat darauf hingewiesen dass sich die Zapfenaussenglieder unter thermischen und chemischen Einflussen verlangern Kurzen wir diese Masse auf die belegte anatomische Lange so haben wir lediglich hinzunehmen dass peripherwarts in der Netzhaut ein zunehmend an den beiden Spektralenden verkurztes Fre quenzband empfangsfahig bleibt sich die zentrale volle Farbtuchtigkeit all mahlich reduziert eine auch durch funktionelle Daten des Auges belegte Tat sache

Das lt Sp 8 im Zentrum der Fovea (0) extrem kurze Frequenzband konnte durch brechungsindexspezifische Einflusse des dort vorhandenen Makulapigments (Xantophyll) oder durch hexagonale kristalline Einlagerung desselben in das Netzhautraster gedehnt werden oder aber die in Fig 12 wiedergegebene Fres nel ebene (z - g /0 82 λ) in der die Periodenverdopplung der gitternaheren Fresnelebenen ausfallt konnte hier mit ihrem bedeutend breiteren Frequ nz band als Empfangsebene dienen

Doppelraster

Über die Doppelrastermodellrechnung erhalten wir zunachst die Moglichkeit eine Symmetrie Wellenlange (555 nm) auf die Zapfenaussenglieder maximal zu modulieren und zu beiden Enden des Spektrums hin eine der Charakteristik der spektralen Empfindlichkeitskurve der Rezeptoren entsprechend reduzierte Modulation zu erhalten Auch ergibt sich die Moglichkeit im Sinne einer stren gen Auslegung des Duplizitatsprinzips der Rezeptoren alternativ ausschliess lich auf Zapfen abzubilden die Stabchen in Interferenzdunkelzonen zu ver lagern Ob beim Ubergang auf skotopisches Sehen in vertikalen Netzhautzonen eine Verlagerung des ER (um einen zonenspezifischen halben Zapfenabstand) oder eine Dickenanderung der Netzhaut (Ruhelage) diese Umschaltung be wirken konnte oder b unterhalb einer bestimmten Belichtungs*intensitatsschwelle* eine interferenzoptische fur die Zapfen uberschwellige Abbildung *uber die* 1 Beugungsordnung in der 1 Fresnelebene (fur die die 0 *Beugungsordnung* len koharenten Untergrund abgibt) noch nicht gewahrleistet sein *mag muss* offen bleiben

Lediglich die Doppelrastermodellrechnung erlaubt einen Vergleich *mit* der anat mischen Netzhautdickenkurve Unsere Daten *in* Sp 11 stimmen mit

Tabelle 1
Gitteroptische Modellrechnung für die Netzhaut des menschlichen Auges (photopisches Sehen temporaler Teil der Netzhaut im horizontalen Meridian) Masse der Spalten 4–11 in nm

Ausgangsdaten					Einzelraster (AR)			Doppelraster		
1	2	3	4	5	6	7	8	9	10	11
0°	7°	1 5	3 3	3 3	9 3	5 1	4 2	7 2	120	1[illegible]
3°	10°	0 38	12 7	6 4	34 1	18 8	15 3	52 5	110	163
5°	12°	0 30	16 0	8 0	52 2	28 8	23 4	80 9	100	181
8°	15°	0 25	18 8	9 4	69 4	38 3	31 1	107 6	100	208
10	17°	0 22	21 0	10 5	84 1	46 4	37 7	130 3	100	230
20	27°	0 12	37 7	12 6	97 9	54 0	43 9	277 0	100	377
30°	37°	0 08	55 8	13 9	85 8	47 3	38 5	267 0	90	357
40°	47°	0 06	75 1	15 0	62 2	34 3	27 9	241 4	70	311
50°	57°	0 03	127 4	15 9	55 6	19 6	16 0	221 1	50	271
60°	67°	0 02	234 0	16 7	14 5	8 0	6 5	157 5	40	198
65°	72°	0 01	330 6	17 4	7 8	4 3	3 5	114 7	30	145

1 = Netzhautort (Neigungswinkel zur Sehachse d h Verbindungslinie Knotenpunkt – Fovea)
2 = Neigungswinkel zur Augenachse (hinterer Pol zwischen Papille und Fovea)
3 = Visuswerte (zentraler Visus bei 0 = 1 5)
4 = Gitterkonstante g im Eingangsraster ER (in Netzhautstreckenmasse umgerechnete photopische Visuswerte)
5 = Gitterkonstante x im Ausgangsraster AR (ortsspezifische Abstandsmasse zwischen Zapfen)
6 = Abstandsmass zwischen AR und z Ebene hinter dem AR (Rezeptorenaussenglieder bene) für λ 430 nm (f Wert)
7 = Abstandmass zwischen AR und z Ebene hinter dem AR für λ 780 nm (f Wert)
8 = Gesamtlänge des Frequenzbands in z Richtung zwischen λ 430 nm und 780 nm (Differenz zwischen den Spalten 6 und 7)
9 = Abstandmass zwischen ER und AR (innerer und äusserer Netzhautgrenz membran) für λ max 555 nm (f Wert)
10 = Zapfenlänge (mechanische Länge im funktionellen Zustand s Text)
11 = Theoretische funktionelle Netzhautdicke E inkl funktioneller Zapfenlänge (Summe der Spalten 9 und 10)

Da die von einzelnen Stäbchen im AR belegten Gitterflächen jedoch lediglich Durchmesser und damit Abstandsmasse von 1 0–1 8 µm erreichen (Zapfenbelegte Flächen hingegen einen ∅ von 1 65–ca 7 2 µm und Abstände lt Sp 5 in Tab 1) bleibt ein über entsprechende Gitterkonstantenmasse in der gitternächsten z Ebene aufgebautes Frequenzband des sichtbaren Spektrums stets

6 embryonalen Entwicklungsmonat erst kommt uber einen durch Bach & Seefelder (1914) belegten Konzentrationsprozess die endgultige Ganglienzellverteilung zustande die i Wesentl durch eine Anhaufung von Ganglienzellen uber der zentralen und eine isopteren zonenspezifisch orawarts zunehmende Reduktion der Ganglienzellen gekennzeichnet ist (Steinbach 1965) Sollten sich im Chorohgerust fixierte Ganglienzellen unabhangig von diesem in der Netzhaut verlagern konnen? Oder hatte die fruhe und dauerhafte Aneinanderkopplung von Ganglienzellen und Gliaraster gerade eine ausschliesslich gemeinsame Verlagerung sicherzustellen die im 6 Monat noch moglich ist weil erst im 7 Monat Rezeptoren aus der Netzhaut auswachsen und diese an der Pigmentepithelschicht verankern? Ein gitteroptisch wirksames radialkonzentrisches Gliaraster und ein in der Ganglienzellverteilung angelegtes rezeptives Feldraster mussten dann unausweichlich gleiche zonenspezifische Masse aufweisen und beide waren – im Sinne von Fig 3 – als komplementar zu betrachten

Diskussion

Eine gitteroptische Modellrechnung kann nur als Naherung gelten und muss eine Reihe von Fragen offenlassen Sie bietet jedoch insbesondre in der Netzhaut Bildebene in der Einfach oder Doppelrastervariante die Moglichkeit den Stabchen ein Helligkeitssignal zuzufuhren und – oberhalb einer bestimmten Belichtungsschwelle und Flachengrosse im zentralen koharenten Fraunhoferschen Beugungsscheibchen in einer Fresnelebene die O Beugungsordnung als koharenten Untergrund fur eine beugungsoptische Abbildung uber die 1 Ordnung zu benutzen die den Zapfen nicht nur eine Tragerwelle sondern spektrale Frequenzbander als Seitenbander zur Modulation anbietet Polarisationsoptische Effekte in den Beugungsgittern konnen hinzukommen Phaseneffekte konnen die Daten zur Netzhautdicke reduzieren Die gitteroptische Behandlung beeinflusst weder die geometrisch optischen Abbildungsgesetzmassigkeiten vor der Netzhaut noch scheint sie mit der Interpretation der Rezeptoren als wave guides unvereinbar eine Gitter Rezeptoren Kombination bietet durch die Moglichkeit zur Frequenz Amplituden oder Phasenmodulation vielmehr eine Reihe zusatzlicher Vorteile Die Verifizierung der gitteroptischen Arbeitshypothese durfte intra vitalmikroskopisch nicht unmoglich sein

W Stoeckenius (1976) konnte zeigen dass die Photosynthesemolekule im *Halobacterium im* Nahbereich hinter hexagonalen Biomembranen in einem geometrischen Verteilungsmuster liegen das auffallig *an* Verteilungsmuster diskreter Interferenzmaxima hinter hexagonalen Gitterkombinationen *erinnert.* Burtt & Catton (1966) versuchten mittels der speziell von Rogers (1962) *mitgeliefert* – gitteroptischen Theorie – den Visuswerten von Insektenaugen auf die *Spur zu* kommen Ein visuelles System in dem – wie im *menschlichen* – uber die In

Straatsma s Daten (1969) darin uberein dass die Netzhautdicke in der Fovea mitte (Straatsma 100 μm) und am Orarand (Straatsma 110 μm) die kleinsten Werte erreicht Bei ca 4–8° temporal der Fovea (Para /Perifovea) belegen Straatsma s Messungen ein Dickenmaximum mit 230 μm (nach andern Autoren bis zu 400 μ) wahrend unsre Rechnung erst weiter peripherwarts (bei 20–40) ein Maximum von ca 360 μm ergibt das zudem eine *in vivo* Zapfenlangung mitenthalt Die rechnerische Netzhaut Dickenverlaufskurve weist somit eine weitgehende Übereinstimmung mit den anatomischen Daten auf Stellt beson ders die innere Grenz membran der Netzhaut ein an Fovea Papille und Ora starker fixiertes Raster dar das – auf den Glaskorper aufgespannt – der Ein wirkung des *in vivo* wirksamen Augeninnendrucks ausgesetzt ist so ist auch die Zone der starksten funktionellen Netzhautverdickung weiter peripherwarts als im anatomischen Zustand zu erwarten (mit ihr konnte die funktionelle Zapfenlängung parallelgehen)

Eingangsraster und rezeptives Feld

Lasst sich histologisch im ER kein Gitter mit Gitterkonstantenwerten der pho topischen Visuswerte bestatigen (und es scheint so als seien Gitterkonstan tenwerte von bis zu 331 μm am peripheren Netzhautrand eine extreme Zumu tung an eine Epithelzellschicht selbst die Pigmentepithelzellen erreichen dort nur Abstande von bis zu 60 μm) so konnte unsre Modellrechnung zumindest bis ca 30° akzeptabel erscheinen Eine Reduktion der g Werte verringert stets die Netzhautdickenwerte und nahert sie noch mehr den anatomischen Werten an Haben die Netzhautdicke und ein mogliches ER hingegen keinerlei Bedeu tung fur die beugungsoptische Lichtmodulation oder Ortsfrequenzfilterung so konnte fur Letztere in der Bildebene nur die rezeptive Feldorganisation der Netzhaut – deren Substrat das konzentrisch organisierte nervose Einzugfeld der Ganglienzellen darstellt – in Frage kommen (Kelly 1975) Die Daten der Sp 4 in Tab 1 (in Netzhautstreckenmasse umgerechnete photopische Visuswerte) scheinen mit der Ganglienzellverteilung gut zu korrelieren Die rezeptive Feld grosse (zugleich Feldmittenabstand) wachst lt Hubel und Wiesel (1960) in der Affennetzhaut z B von 4 (ca 18 μm) bei 4° auf 2 (ca 360 μm) in Oranahe (unsre Daten lauten bei 5 = 16 μm bei 65 = 331 μm) Die Zahl der in einem rezeptiven Netzhautfeld zusammengeschalteten Zapfen betruge entsprechend der auf Flachen umrechenbaren Daten in Sp 4 und 5 (Tab 1) zentral bei 0° – 4 bzw 7 Zapfen – ein auch von Oppel (1966) fur wahrscheinlich ange sehener Schaltplan – in Oranahe bis zu ca 270 Zapfen

Dennoch gilt entwicklungsgeschichtlich zugleich Folgendes in der Embryo nalentwicklung differenzieren die zunachst in 2–3 Zellagen gleichmassig in der Netzhaut verteilten Ganglienzellen im Netzhaut Gliarohgerust in dem sie selbst wie ihre fruh papillenwarts auswachsenden Sehnerven durch Fibrillen fixiert sind als Erste unter den der Retina eingelagerten nervosen Zellen Im

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vagination eines Flächenepithels die Verlagerung einer Gitter Rezeptoren Kombination in die Fokusebene eines akkomodationsfähigen optischen Systems erreicht wird dürfte in Signal und Informationsvorverarbeitung neue Möglichkeiten eröffnen (z B die Auswertung der in parallaktischen Strahlenkegelanteilen enthaltenen Information zur monokularen Entfernungsmessung und Akkomodationsscharfstellung) auch wenn oder gerade weil es dieselben bewährten Bauelemente andrer biologischer visueller Systeme verwendet

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Beta-Adrenoceptor Antagonism and Intraocular Pressure

A Clinical Study on
Propranolol Practolol and Atenolol

by

Karin Wettrell

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From the Department of Ophthalmology

Malmö General Hospital University of Lund Malmö Sweden

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"Remember how much you do not know

Do not pour strange medicines into your patients"

Sir William Osler 1849 – 1919

English revised by L James Brown

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INTRODUCTION

The differences in response in vitro and in vivo of a variety of tissues to five sympathomimetic amines led Ahlquist (1948) to introduce the concept of two types of adrenergic receptors He classified them as α- and β-receptors α-receptors mediate contraction of smooth muscles, such as those of the blood vessels of skin and mucosa, gastrointestinal sphincters and iris Stimulation of β-receptors is followed by increase in heart rate and cardiac contractility and relaxation of smooth muscles in blood vessels of striated muscles bronchi uterus and ciliary body (Conolly et al 1976) Lands et al (1967) found that β-receptors did not have the same properties in different organs They proposed two subgroups of β-receptors The ones mediating cardiac acceleration and lipolysis were termed β_1 and receptors responsible for broncho- and vasodilatation were termed β_2

The first specific β-adrenoceptor blocking drug dichloroisoproterenol (DCI) was introduced by Powell and Slater (1957 1958) Their discovery initiated the development of similar compounds and the first therapeutically useful β-adrenoceptor antagonist propranolol (structural formula in Fig 1) was presented in 1964 (Black et al 1964 1965) Since then several clinically employable β-adrenergic blocking drugs have become available which all possess a competetive reversible inhibition of the β-receptor sites (Conolly et al 1976) However the various β-blocking compounds differ in other properties such as cardio-(β_1)-selectivity intrinsic sympathomimetic activity and membrane-stabilising effect

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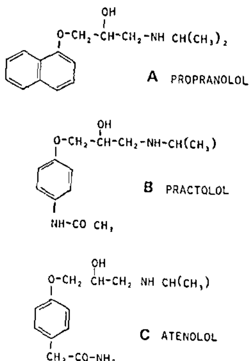


Fig 1 Structural formulae of A propranolol B practolol and C atenolol

The first substance found to selectively inhibit the cardiac-(β_1)-receptors and thus to lend further support to the theory proposed by Lands et al (1967) was practolol (structural formula in Fig 1) (Dunlop and Shanks, 1968) Recently other β-blocking substances with this property have been synthetized, such as atenolol (structural formula in Fig 1) (Barrett et al 1973) Their selectivity is however not absolute since large doses of e g practolol cause β_2-inhibition (Lertora et al 1975)

In addition to their inhibitory effect many β-blockers also have an agonistic effect on the β-receptors (intrinsic sympathomimetic activity or ISA) β-inhibitors with ISA are, for instance, practolol, oxprenolol and pindolol Substances lacking these characteristics are, for example, propranolol

atenolol and timolol

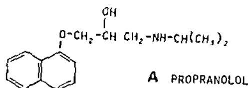
Furthermore several β-blocking compounds also have a membrane-stabilising activity (synonymous quinidine-like or local anaesthetic effect) which is separate from the β-adrenergic inhibition Propranolol has been reported to possess local anaesthetic activity (Morales-Aguilerá and Vaughan Williams 1965) whereas practolol and atenolol have been found to lack this property (Dunlop and Shanks, 1968 Barret et al 1973)

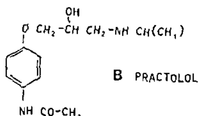
The properties of the β-adrenoceptor antagonists investigated in this study may be summarized as follows

Substance	β_1-selectivity	ISA	Local anaesthetic effect
Propranolol	-	-	+
Practolol	+	+	-
Atenolol	+	-	-

Effect of β-adrenoceptor blocking drugs on intraocular pressure (IOP)

The first report on the ability of β-adrenoceptor blocking substances to decrease the IOP was published by Phillips et al in 1967 They found a reduction in IOP in 7 patients with glaucoma treated intravenously with 10 mg propranolol In one patient the fall in tension persisted during sustained oral treatment Subsequent clinical investigations using intravenous and oral propranolol in different doses corroborated their finding (El Shewy and min 1969 Vale and Phillips 1970 Sharaf et al 1974) Also reports concerning the therapeutic use of oral pro-





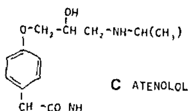


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Only a few publications are available on the influence of practolol on IOP (Vale and Phillips, 1973, Hagedoorn and Tjoa 1974) The undesirable side-effects of practolol the so-called oculomucocutaneous syndrome, (see p 41) have limited clinical trials with the drug

Atenolol, another selective β_1-inhibitor, was introduced some years ago The substance has no local anaesthetic properties, which makes it suitable for topical application Atenolol eye drops have recently become available for clinical use

The present study was prompted by the preliminary reports of the usefulness of β-blocking substances in the treatment of glaucoma (Öhrström, 1973, Pandolfi and Öhrström, 1974) and of the development of new β-blocking drugs

AIMS OF THE STUDY

The investigation concerns mainly the ability of different β-adrenoceptor blocking drugs both cardio-($β_1$)-selective inhibitors such as practolol (Eraldin®) and atenolol (Tenormin ICI 66082), and non-selective inhibitors such as propranolol (Inderal®) to reduce IOP in man Efforts were made to

1 establish the time-course and dose-response relationship of the decreasing effect of systemic propranolol on IOP (I)

2 compare the IOP reducing ability of systemic propranolol with that of pilocarpine and to determine whether their effects were additive (II)

3 estimate the effect of systemic propranolol on IOP in healthy volunteers and compare this effect with that of selective $β_1$-blocking compounds (practolol and atenolol) (III)

4 find out whether the decrease in IOP induced by these drugs is due to changes in the episcleral venous pressure and estimate the possible influence of β-blocking substances on the decrease in IOP following repeated tonometry (IV VI)

5 ascertain whether a topically administered selective $β_1$-blocking drug (atenolol) could reduce IOP and if so to assess the time-course and dose-response relationship (V);

6 compare the influence on IOP of topical atenolol with that of pilocarpine and study the additive effect if any (VI)

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Drugs

Propranolol (Inderal®)

Tablets 20 40 and 80 mg

Practolol (Eraldin®)

Tablets, 100 mg

Atenolol (Tenormin ICI 66082)

Tablets 100 mg which were divided into halves

Eye drops in concentrations of 1, 2 and 4% The drops were prepared by ICI Pharmaceuticals Benzalkonium chloride (0 02% w/v) was used as a preservative and the pH was adjusted to 6 0

Pilocarpine

Eye drops were prepared by the local pharmacy at the Hospital of Malmö and contained pilocarpine chloride 2% methylhydroxybenzoate 0 04% propylhydroxybenzoate 0 02% and saline 0 9%

Placebo

Propranolol placebo tablets were supplied by ICI Pharmaceuticals Placebo eye drops had the same composition as atenolol and pilocarpine eye drops respectively except that they did not contain atenolol or pilocarpine Atenolol placebo was supplied by ICI Pharmaceuticals and pilocarpine placebo by the local pharmacy at the Hospital of Malmö

Clinical Material

Healthy volunteers (III, IV)

Seventeen healthy volunteers (15 women and two men), aged 18-47 (mean 29) took part in the study Some of the women participated in more than one trial

Patients with ocular hypertension (I, II, V, VI)

The total number of patients participating in the studies was 32 (23 women and 9 men), aged 32-77 (mean 62) Some patients participated in more than one trial All 32 had an IOP $\geq$ 22 mm Hg, normal visual fields according to Goldmann perimetry and no demonstrable glaucomatous involvement of the optic discs Twenty-two patients were receiving treatment with pilocarpine, which was withdrawn at least 24 hours, and in most cases 48 hours, before the trial One patient was receiving pilocarpine + physostigmine and another systemic propranolol (160 mg/day), both substances were withdrawn 48 hours before the study None of the 32 patients had any history of asthma, bronchospasm cardiac failure or other disorders contraindicating administration of β-adrenoceptor blocking drugs and none was given adrenergic drugs during the trial The patients were examined with ECG to ascertain whether they were acceptable for the study

Ethical standards according to the ethical committee at the University of Lund were observed and informed consent was obtained from the patients

The doses were as follows

Propranolol 40 mg x 2

Practolol 100 mg x 2

Atenolol 50 mg x 2

Study V

Atenolol eye drops in concentrations of 1 2 or 4% and placebo eye drops were applied in a randomised double-masked cross-over manner Each person received the three concentrations of atenolol and placebo eye drops with intervening drug-free intervals of at least 48 hours

In the single-dose study one drop of either atenolol or placebo was instilled into the conjunctival sac of each eye by an ophthalmic assistant

In the multiple-dose study the patients were instructed to instill 1-2 drops of either atenolol or placebo in both eyes at 7 a m noon and 7 p m on 7 consecutive days

Study VI

Atenolol (2%) pilocarpine (2%) and placebo eye drops were studied in a randomised double-masked cross-over manner The patients were instructed to instill the eye drops (1 drop in each eye) from two coded bottles with an interval of 15 minutes at 7 a m 1 p m and 7 p m on 14 consecutive days The drug-free interval between two consecutive trial periods was always at least 8 hours

Methods

Administration of drugs

Study I

A single dose of placebo and propranolol (20, 40 or 80 mg) was given by mouth to two groups of six patients who had fasted for 12 hours The first group (A) consisted of patients with an IOP of 20 to 29 mm Hg and the second group (B) of patients with an IOP of 30 to 39 mm Hg Two hours later a light lunch was served Placebo and propranolol were tested at intervals of at least 48 hours The trial was performed in a single-masked manner with the patients being unaware of the dose received Each patient received placebo and the three doses studied

Study II

The investigation was performed in a randomised double-masked cross-over manner utilising the double dummy technique The patients were instructed to take one tablet (either 40 mg propranolol or placebo) at 7 a m and 7 p m and instill the drops (either 2% pilocarpine or placebo), one drop in each eye at 7 a m , noon and 7 p m on 7 consecutive days The drug free intervals between the treatment periods were at least 48 hours

Studies III and IV

Propranolol, practolol and atenolol were given by mouth in two equal doses, one at 7 a m and the other at 7 p m

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Intraocular pressure

The applanation tonometer of Goldmann was used The tonometer was calibrated daily Before the tonometry 1-2 drops of Fluress® (Pharmacia AB, Uppsala, Sweden), a mixture of oxibuprocaine hydrochloride and sodium fluorescein, were instilled into the conjunctival sac

Before treatment was started the IOP was recorded at 8 a m , noon and 4 p m (II, III, V, VI)

Single-dose study

The IOP was measured in both eyes one hour before and once an hour for 6 hours after administration of placebo or oral propranolol (I) The IOP was recorded in the same manner 0 5, 1, 1 5, 2, 3, 4 and 7 hours after instillation of one drop of atenolol or placebo (V)

Multiple-dose study

The IOP was measured regularly at the same time of the day, i e at noon (II, III, V, VI) or 4 p m (IV) Measurements were made on the 1st, 2nd, 5th and 8th day of treatment in study III In papers II and V the recordings were made on the 1st and 7th days and the 1st, 4th and 7th days, respectively In paper VI the measurements were made on the 2nd, 7th and 14th day IOP was measured at 4 p m on the second day of treatment in paper IV

The last day of treatment the IOP was recorded also at 8 a m and 4 p m (II, III V VI)

Blood pressure and heart rate

The systemic blood pressure and heart rate were measured after the subjects had been lying down for about five minutes The systolic and the diastolic pressure were measured with a mercury Erkameter (II V) or an aneroid (Minimus) sphygmomanometer, which had previously been calibrated at the local department of medicine (I III IV) All measurements were made at the same time of day

Pupil size (III V)

The diameter of the pupil was measured in standard illumination with the pupillometer in Goldmann s perimeter All measurement were made at the same time of day

Episcleral venous pressure (IV VI)

In two of the present studies the episcleral venous pressure (Prv) was studied with the method described by Krakau et al (1973) In this method the actual vessel is compressed by a jet of air whose pressure is increased until the vessel is occluded (that is +++ effect) The results are expressed in mm Hg

The measurements were made on a so-called recipient vein i e an episcleral vein which had just received a large aqueous vein or an ordinary episcleral vein In a given eye the measurements were always made on the same vessel Three consecutive values of the +++ effect were measured All recordings were made with the subjects sitting after application of 1-2 drops of oxibuprocaine hydrochloride 0 4% The actual venous pressure is about 3-4 mm Hg lower than the +++ value (Krakau et al 1973)

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The last day of treatment the IOP was recorded also at 8 a m and 4 p m (II, III V VI)

RESULTS

Reduction of elevated intraocular pressure by systemic propranolol (I II)

Single-dose study

Propranolol was given in a single oral dose of 20 40 and 80 mg respectively to two groups of 6 patients each with untreated IOP of 20 to 29 mm Hg (Group A) and of 30 to 39 mm Hg (Group B)

A reduction in IOP was demonstrable by 1 hour This decrease was statistically significant by 1-2 hours and reached a maximum by 3 hours in both groups The mean maximum IOP falls after 20 40 and 80 mg were 6 2 6 9 and 8 5 mm Hg respectively in group (A) The corresponding decrease in group (B) were 5 8 7 8 and 9 8 mm Hg

The absolute fall in IOP was greater in patients with an initially higher IOP (Fig 2)

The reduction in IOP seemed to be dose-related with statistical confirmation in group (B) (Figs 2 and 3)

Multiple-dose study

Propranolol (40 mg twice a day) was given orally to 8 patients with untreated IOP $\geq$ 22 mm Hg The IOP decreasing effect of systemic propranolol on the IOP was compared with that of pilocarpine 2% three times a day) with a double-masked cross-over method using the double dummy technique

A mean fall of 5 4 mm Hg compared with that after the placebo was observed at noon on the first day of treatment The decrease was statistically significant (p< 0 01) The reduction

determined at 4 p m (IV) In the study reported in paper VI Prv was estimated before, and at the end of, each period of treatment at 2 p m

Repeated tonometry (IV)

The Goldmann applanation tonometer was used The IOP of the left eye was recorded and immediately afterwards that of the right eye, and then once a minute for five minutes Finally the IOP of the left eye was recorded again at the end of the five minute period The measurements were all made at the same time of day (around 4 p m)

Corneal sensitivity (V)

The sensitivity of the cornea was assessed with Cochet and Bonnet's aesthesiometer (Cochet and Bonnet, 1960) The measurements were performed at noon on the 1st, 4th and 7th day of treatment

Calculations

The results are generally presented as mean values ± S E M but individual data are occasionally given in figures The level of significance of differences between results was estimated with the Student's t-test either for paired or unpaired observations (I, II, IV, V, VI) In paper III the one-sided sign test was used In four of the present studies (I, II V and VI) the results obtained during treatment with active substance and placebo were compared All differences with a probability less than 0 05 were considered significant

persisted during the trial and on the 7th day of treatment it was 4 3 mm Hg (p< 0 05) Pilocarpine seemed to reduce IOP to about the same extent as oral propranolol (Table I)

Propranolol combined with pilocarpine decreased the mean IOP more than did pilocarpine alone On the first day of treatment pilocarpine and pilocarpine + propranolol reduced the mean IOP by 1 3 and 5 2 mm Hg respectively This difference was significant (p< 0 01) The additive depressive effect of propranolol persisted throughout the period of treatment (Table I) At 8 a m and noon on the 7th day of treatment the decrease caused by propranolol + pilocarpine was still significantly larger than that produced by pilocarpine alone

TABLE I

Mean IOP (mm Hg) _ S E M of 8 pat ents after 7 days treatment w th placebo pilocarpine propranolol and pilocarpine propranolol (cti e substance compared th placebo) Statistical sign ficance expressed as (p< 0 05) (p< 0 01) (p< 0 001)

Substanc	No of patients	8 a m	noon	4 p m
Untreated	8	2 3 1 94	25 9 1 71	24 3 1 01
Placebo	8	24 5 1 46	24 6 1 56	23 u + 1 26
Pilocarpine	8	20 7 1 0	22 0 0 80	19 9 0 91
Propranolol	8	19 2 1 09	20 3 1 31	20 2 _ 0 87
Pilocarpine propranolol	8	18 8 1 28[x]	19 9 + 1 04	19 3 0 63

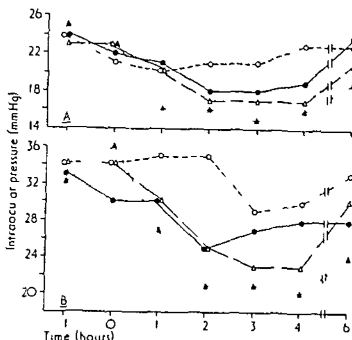


Fig 2 The time-course of the IOP response in two cases, one from group (A) and one from group (B), recorded from the eyes with the highest IOP after treatment with placebo and different doses of propranolol The substances were administered at T = 0 hour Placebo (o—o), 20 mg propranolol (●—●), 40 mg propranolol (Δ—Δ), 80 mg (▲—▲) (A) Initial highest IOP ranging 20 to 29 mm Hg (B) Initial highest IOP ranging 30 to 39 mm Hg

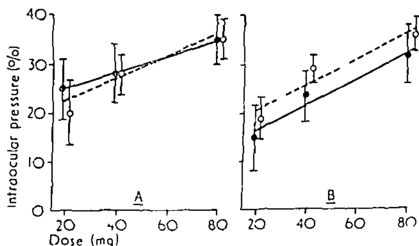


Fig 3 Mean maximum IOP decrease ± S E [illegible] after administration of different doses of propranolol Initial highest IOP ranging 20 to 29 mm hg (●—●) Initial highest IOP ranging 30 to 39 mm Hg (o---o) (A) Eye with the highest IOP (B) Fellow eye

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Mean IOP (mm Hg) S E M of 8 pati nts after 7 day treatment with pl cebo pilocarpine propranolol and pilocarpine propranolol (acti substance compared with placebo) statistical significance expressed as (p< 0 05) (p< 0 01) (p< 0 001)

Substance	No f patients	8 a.m	noon	4 p m
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Placebo	8	24 5 1 46	24 6 1 56	23 6 + 1 26
Pilocarpine	8	20 7 1 20	22 0 + 0 80	19 9 0 91
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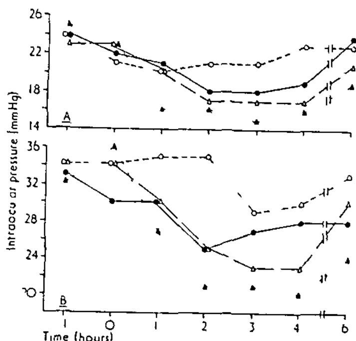


Fig 2 The time-course of the IOP response [illegible] two cases, [illegible] from group (A) and one from group (B), recorded from the [illegible] with the highest IOP after treatment with placebo and different doses of propranolol The substances were administered at T = 0 hour Placebo (o—o), 20 mg propranolol (●—●), 40 mg propranolol (Δ—Δ), 80 mg (▲—▲) (A) Initial [illegible] IOP ranging 20 to 29 mm Hg (B) Initial [illegible] IOP [illegible] [illegible]0 to [illegible]9 mm Hg

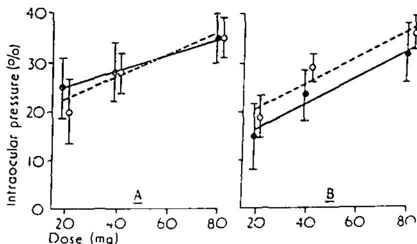


Fig 3 Mean maximum IOP decrease ± S E [illegible] administration of different doses of propranolol [illegible] highest IOP ranging 20 to 29 mm Hg (●—●) [illegible] IOP ranging [illegible]0 to [illegible]9 mm Hg (o---o) (A) Eye with the [illegible] IOP (B) Fellow eye

Also in another trial (IV) the same substances were found to cause a significant fall in IOP on the second day of treatment with one exception (left eye in the group treated with atenolol)

Reduction of elevated intraocular pressure by topical atenolol (V VI)

Single-dose study

Atenolol in three concentrations of 1 2 or 4% was instilled as a single dose (one drop in each eye) into the conjunctival sacs in 8 patients

Each concentration caused a significant fall ($p < 0\ 05 - 0\ 001$) in IOP within 1 hour The reduction was greatest by 2-3 hours and disappeared by 7 hours The mean maximum falls after installation of 1 2 and 4% atenolol were 4 9, 6 1 and 6 3 mm Hg respectively (Fig 4)

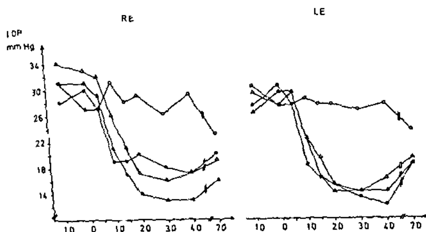


Fig 4 Duration of IOP response of one patient after treatment with placebo and different concentrations of atenolol The formulation were administered at T = 0 hour Placebo (o—o) Atenolol 1% (•—•) (Δ—Δ) 4% (▲—▲) RE = right eye LE = left eye

Reduction of intraocular pressure by systemic propranolol, practolol and atenolol in healthy volunteers (III, IV)

Propranolol, practolol and atenolol were given orally to 3 groups in doses of 80, 200 and 100 mg/day, respectively The 3 groups consisted of 8 persons (III) and 6 persons (IV), respectively

In the present study (III) each of the 3 drugs caused a demonstrable reduction in the mean IOP on the first day of administration The effect persisted throughout the 8 day period of treatment The decrease produced by each compound was statistically significant (p< 0 01) compared with untreated IOP values (Table II) No significant differences were found between the IOP falls caused by the different compounds

TABLE II

Mean IOP (mm Hg) of 8 healthy volunteers before and during treatment with propranolol practolol and atenolol (S E M ranging from 0 5 to 1 66) Significance calculated by one-sided sign test

Substance	No of subjects	Eye	Time (in days) 0	1		5	8	Statistical significance
		R	17 8	13 4	13 6	14 4	13 4	p 0 01
Propranolol	8	L	16 6	13 0	13 6	14 1	13 1	p< 0 01
		R	16 5	12 0	12 1	2 5	13 2	p< 0 01
Practolol	8	L	15 8	11 9	11 1	12 5	12 7	p 0 01
		R	16 5	12 5	13 1	12 5	1 1	p< 0 01
Atenolol	8	L	16 0	11 8	13 0	12 3	11 7	p< 0 01

TABLE IV

Mean variation in mean IOP values t noon (mm Hg) + S E M f 8 patients during topical treatment with pilocarpine (2%) atenolol (2%) or pilocarpine + tenolol (active substance compared with placebo) Stati tical significance expressed as (p 0 05) (p 0 01)

Substance	No f patients	Day 2	Day 7	Day 14
Pilocarpine	8	1 5 1 03	2 1 _ 0 75	- 2 3 + 0 88
Atenolol	8	1 4 1 45	2 9 _ 1 03	- 1 6 0 56
Pilocarpine tenolol	8	3 3 1 35	3 8 1 21	3 3 + 0 80

Treatment with combined pilocarpine and atenolol lowered the IOP more than either substance alone although the difference was not statistically significant with one exception (atenolol compared with atenolol + pilocarpine on the 14th day of treatment)

Effect of systemic propranolol practolol and systemic and topical atenolol on the episcleral venous pressure (IV VI)

Given systemically neither propranolol (80 mg/day) practolol (200 mg/day) nor atenolol (100 mg/day) affected the pressure in the episcleral veins as measured on segments just after the entry of aqueous veins (Table V)

Neither did topical atenolol (2% three times a day) alone or combined with pilocarpine (2% three times a day) have any effect on the episcleral venous pressure in patients with elevated IOP

Multiple-dose study

Atenolol in concentrations of 1, 2 or 4% was instilled three times a day to 10 patients for 7 days (V) 2% atenolol and 2% pilocarpine were administered three times a day either alone or combined to 8 patients (VI)

From the first day of treatment each concentration produced a significant decrease in the mean IOP The reduction at noon was 2 4, 2 6 and 3 4 mm Hg for 1, 2 and 4% atenolol, respectively This fall tended to diminish but was still significant at 8 a m and noon after one week's treatment (Table III)

TABLE III

Mean IOP (mm Hg) ± S E M of 10 patients after 7 days treatment with placebo or atenolol in different concentrations (active substance compared with placebo)
statistical significance expressed as (p< 0 05) (p 0 01) (p< 0 001)

	No of eyes	8 a m	noon	4 p m
Untreated	0	25 9 + 0 80	4 0 + 0 61	23 0 0 73
Placebo	0	24 9 ± 0 87	2 8 0 66	2 1 0 77
1% Atenolol	20	22 2 0 60	21 2 0 88	20 0 56
2% Atenolol	0	22 4 + 0 57	20 8 0 54	1 4 0 73
4% Atenolol	18	23 3 C 7(	0 6 0 50	u 8 0 61

Pilocarpine (2% three times a day) and atenolol (2% three times a day) caused a reduction in IOP of roughly the same extent The reduction was significant on the 7th day of treament (noon) and persisted throughout the 14 day period of treatment (Table IV)

TABLE IV

Mean variation in mean IOP values at noon (mm Hg) + S E M f 8 patients during topical treatment with pilocarpine (2%) atenolol (2%) or pilocarpine + atenolol (active substance compared with placebo) Statistical significance expressed as (p 0 05) (p 0 01)

Substance	No of patients	Day 2	Day	Day 14
Pilocarpine	8	1 5 1 03	- 2 1 + 0 7	3 ± 0 88
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Mean IOP (mm Hg) ± S E M of 10 patient after 7 days treatment with placebo or atenol l in different concentrations (active substance compared with placebo) statistical signi icance expressed as (p< 0 05) (p 0 01) (p< 0 001)

	No of eyes	8 a m	noon	4 p m
Untreated	20	25 9 0 80	4 0 0 61	23 0 0 1
Placebo	20	24 9 0 87	2 8 0 66	1 0
1% Atenolol	0	22 2 0 60	21 2 0 68	0 7 0 56
% Atenolol	20	22 4 0 57	0 8 0 54	1 4 0 73
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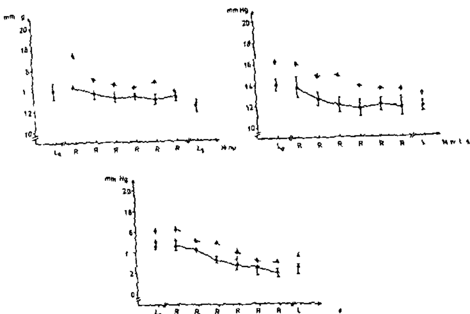


Fig 5 The mean IOP ± S E M before (——) and during (——) treatment with propranolol (•) practolol (o) and atenolol (▲) L_o - initial IOP in the left eye L_5 = IOP after 5 min R_o R R^o - OP in the right eye once a minute for 5 min

Effect of systemic propranolol practolol and systemic and topical atenolol on other ocular parameters

Refraction (III VI)

No consistent changes of refraction were observed in healthy volunteers during treatment with systemic propranolol (80 mg/day) practolol (200 mg/day) or atenolol (100 mg/day) Nor were any such changes found in patients treated with topical atenolol (2% three times a day)

TABLE V

Mean episcleral venous pressure before and during treatment with propranolol practolol a atenolol

Substance	No of subjects	Mean values of +++ effect in mm Hg + S E M	
		Before treatment	During treatment
Propranolol	6	12 8 ± 0 27	12 7 ± 0 22
Practolol	6	13 4 ± 0 14	13 4 _ 0 25
Atenolol	6	13 3 + 0 50	13 0 _ 0 53

Effect of systemic propranolol, practolol and atenolol on the intraocular pressure response following repeated tonometry (IV)

Diminution of the response of the IOP following repeated tonometry was demonstrable during administration of propranolol (80 mg/day) practolol (200 mg/day) and atenolol (100 mg/day) in 6 healthy volunteers, respectively Such a suppression of the response was significant only during treament with propranolol (Fig 5)

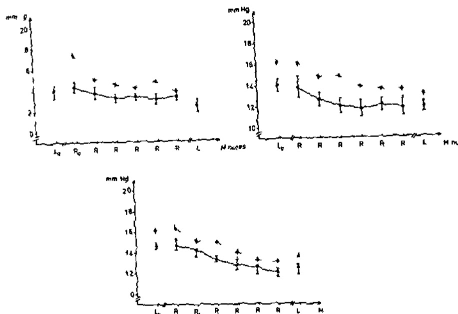


Fig 5 The mean IOP ± S E M before (—) and during (—) treatment with propranolol (•) practolol (o) and atenolol (▲) L_o initial IOP in the left eye L_5 = IOP after 5 mn R_o R_1 ... IOP in the right eye once a minute for 5 mn

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No consistent changes of refraction were observed in healthy volunteers during treatment with systemic propranolol (80 mg/day), practolol (200 mg/day) or atenolol (100 mg/day) Nor were any such changes found in patients treated with topical atenolol (2% three times a day)

Pupil size (III, V)

The size of the pupil in healthy volunteers was not influenced by systemic propranolol (80 mg/day), practolol (200 mg/day) and atenolol (100 mg/day)

Neither did topical atenolol in concentrations of 1, 2 or 4% affect the diameter of the pupil of patients with elevated IOP in short-term studies

Corneal sensitivity (V)

No change in the corneal sensitivity was demonstrated during one week's treatment with topical atenolol in concentrations of 1, 2 or 4%

Effect of propranolol, practolol and atenolol on heart rate and systemic blood pressure (I, II, III, IV, V)

Heart rate

Systemic propranolol caused a significant fall in heart rate both in patients and healthy volunteers The decrease was demonstrated 1 hour after administration of a single dose of 20, 40 or 80 mg and reached its maximum by 2 hours The reduction caused by 40 and 80 mg was significant in patients with elevated IOP During administration of propranolol (80 mg/day) on 7 consecutive days the heart rate remained significantly reduced in patients with ocular hypertension

Systemic propranolol (80 mg/day) caused a significant reduction after 2 days treatment also in healthy volunteers Practolol (200 mg/day) seemed not to influence the heart rate in the healthy volunteers studied Systemic atenolol (100 mg/day),

however, diminished the heart rate significantly in the healthy volunteers investigated

Topical atenolol in concentrations of 1,2 or 4% did not affect the heart rate

Systemic blood pressure

A single dose of 20 40 or 80 mg propranolol did not produce any significant decrease in the systemic blood pressure, with one exception (systolic blood pressure 3 hours after administration of 40 mg) In multiple-dose studies systemic administration of propranolol (80 mg/day) was followed by a reduction of the systolic blood pressure and though to a lesser degree also of the diastolic blood pressure in healthy volunteers as well as in patients In most studies this decrease was significant In one of the studies (III) practolol was followed by a significant fall in systolic blood pressure in the healthy volunteers but not in another (IV) (Table VI) In both the investigations of healthy volunteers systemic atenolol caused a significant fall of the systolic blood pressure

No change in the systemic blood pressure was however, observed during topical application of atenolol in concentrations of 1 2 or 4%

Pupil size (III, V)

The size of the pupil in healthy volunteers was not influenced by systemic propranolol (80 mg/day), practolol (200 mg/day) and atenolol (100 mg/day)

Neither did topical atenolol in concentrations of 1, 2 or 4% affect the diameter of the pupil of patients with elevated IOP in short-term studies

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DISCUSSION

Effect on intraocular pressure

Propranolol

The ability of systemically administered propranolol to reduce IOP has been known for a decade (Phillips et al 1967) The present study confirms this property both in patients with elevated IOP and in healthy volunteers The effect of oral propranolol on IOP was dose-dependent in patients with a tension ranging from 30 to 39 mm Hg (I) a finding confirmed by Takase (1976) But Vale and Phillips (1970) found no such dependency when the drug was given intravenously This difference between oral and intravenous administration can be explained by the fact that Vale and Phillips (1970) gave two different doses, one soon after the other with the result that the second and larger dose was given when the IOP was already reduced and a further decrease proportional to the second dose could hardly be expected

As observed by Cote and Drance (1968), the absolute fall in IOP appeared to be greater in patients with higher pretreatment values Furthermore Borthne (1976) demonstrated a correlation between the pressure fall and the pretreatment IOP value

In the present investigation a reduction in IOP was observed 1 hour after administration of 20 40 or 80 mg propranolol, with a maximum effect by 3 hours which persisted 6 hours after administration of the larger doses According to Cuthbert and Collins (1975) the plasma level after a single oral dose of propranolol (40 mg) is at its highest 2-3 hours after administration The maximum degree of β-adrenoceptor blockade occurred at

TABLE VI

an sy temic blood pressure and pulse r te in healthy oluntour befor and during treatment with propranolol actol l and atenolol

bstance	No f sub-jects	Mean sy t blood pressur in mm Hg S E M		Stati tical signif cance	Mean di t blood pressure in mm Hg S E M		Stati tical ignificance	Mean pulse rate in beats per min S E M		Stati tical ignif cance
		Befo e treat ment	During treat ment		Befor treat ment	During treat ment		Befor treat ment	During treat ment	
opranolol	6	119 3 21	108 2 79	p 0 01	81 2 39	76 2 01	p 0 05	65 2 51	56 3 8	p 0 01
actolol	6	116 2 39	113 1 67	NS	74 3 00	73 2 14	NS	67 4 97	63 3 00	NS
enolol	6	124 2 01	108 3 33	p 0 01	77 1 67	0 2 87	p< 0 05	73 3 81	59 3 96	p< 0 01

2 mg propranolol intravenously we found a decrease of IOP in healthy volunteers treated with oral propranolol (80 mg/day) (III IV) This reduction was observed on the first day of treatment and persisted throughout the 8 day period of the study The decrease in IOP seemed to be fairly constant during the day, an observation reported also by Borthne (1976) in patients with glaucoma

Practolol

The literature on the influence of practolol on IOP is scanty In a short term study Vale and Phillips (1973) observed a significant fall in IOP in 6 patients out of 8 during treatment with topical practolol (10%), a decrease comparable to that achieved during treatment with 1% propranolol eye drops In a patient with glaucoma and heart disease Hagedoorn and Tjoa (1974) incidentally noticed that oral practolol (300 mg/day) reduces IOP

In the present investigation (III IV) oral practolol (200 mg/day) reduced the IOP in healthy volunteers to roughly the same degree as oral propranolol (80 mg/day) The reduction observed persisted throughout the 8 day period of treatment

Atenolol

Recent double-masked trials have shown that oral atenolol in a single dose of 50 mg can significantly reduce an elevated IOP (Elliot et al 1975 Macdonald et al 1976 1977) According to Macdonald et al (1976) atenolol has a stronger effect than an equivalent dose of propranolol Macdonald et al (1977) also found that the effect of 50 mg oral atenolol was at least equal to that of 500 mg acetazolamide and that combined treatment with

approximately the same time However, since oral propranolol undergoes hepatic metabolism with conversion of the drug to active metabolites (Fitzgerald and O'Donnel, 1971), the drug plasma level may not reflect the total β-inhibitory effect of the substance

Oral propranolol (80 mg/day) and pilocarpine (2% three times a day) seemed to be equally effective in reducing IOP (II) In a previous investigation (Drance and Nash, 1971) 2% pilocarpine reduced the IOP with a maximum of 4 mm Hg Five hours after instillation of the drug the IOP remained decreased by about 2 5 mm Hg, which is in fair agreement with the present results (1 3 mm Hg decrement compared with that after placebo) The fall in tension 5 hours after administration of 40 mg propranolol was 5 4 mm Hg, which is in good agreement with our investigation (I) The IOP decrease following administration of propranolol was significantly larger than that following instillation of pilocarpine on the first day of treatment The difference tended to persist after one week's treatment, but it was not significant

Combined pilocarpine and propranolol lowered the IOP more than pilocarpine alone A similar additive effect of oral propranolol was also reported by Borthne (1976) in patients previously treated with pilocarpine or pilocarpine + acetazolamide Furthermore, the beneficial effect on IOP of oral propranolol in patients not adequately controlled by conventional antiglaucomatous therapy was also confirmed in clinical trials by Öhrström (1973) and Pandolfi and Öhrström (1974) Also Bietti (1972) and Bietti et al (1972) found an additive effect of topical propranolol in combination with pilocarpine

Like Sharaf et al (1974) who reported a fall in IOP after

than 1% Similar results have been obtained by Bucci et al (1972) with propranolol They found that 3 and 4% propranolol did not reduce the IOP more than 2% propranolol But Zimmerman and Kaufman (1977 b) described a dose-relationship for timolol, a non-selective β-adrenergic antagonist without ISA or local anaesthetic effect in concentrations of 0 1% 0 25% and 0 5% Increasing the concentration to 1% did not cause further reduction Timolol is a β-adrenergic blocking drug which has been shown to be approximately 8 times more potent than propranolol (Zimmerman and Kaufman 1977 a) This higher potency was also reflected by its prolonged effect on the IOP

In the multiple-dose study in which atenolol was applied topically 3 times a day (V) a significant fall in the IOP was demonstrated from the first day of treatment However this hypotensive effect tended to diminish during the period of treatment (7 days) but statistical significance of all the concentrations persisted A similar phenomenon has been described by Phillips et al (1977) who found 4% atenolol to be more effective during the first 12 hours than later A tendency to tachyphylaxis was also described by Krieglstein et al (1977) in patients receiving bupranolol A partial loss of action was observed within 4 days of repeated treatment with the drug The ocular hypotensive effect could however still be demonstrated after 14 days' treatment with atenolol (VI) In this study atenolol (2% three times a day) lowered the IOP in patients with ocular hypertension to the same extent as pilocarpine (2% three times a day) during the 14 day period of application Combined atenolol and pilocarpine was followed by a greater decrease in IOP than administration of either drug alone This is in agreement with the publications of

atenolol and acetazolamide lowered the IOP more than either substance alone

In the present study atenolol reduced the IOP also in healthy volunteers (III, IV) In one of these investigations (III) the decrease was demonstrable from the first day of treatment and comparable to that observed during treatment with propranolol and practolol Although the absolute IOP values during treatment with atenolol seemed to be lower than those during treatment with propranolol, the difference was not significant The fall in tension persisted during the treatment period of 8 days

Atenolol eye drops have been available for clinical use for only some 18 months Atenolol (4%) was found to produce a highly significant decrease of the IOP in patients with ocular hypertension, a finding corroborated by Phillips et al (1976, 1977) in healthy volunteers and in patients with glaucoma The decrease in the present study (V) was observed by 1 hour with a maximum fall (6 3 mm Hg) by 2-3 hours A similar time-course and maximum fall have also been described after other topically applied β-adrenoceptor antagonists, such as pindolol, oxprenolol (both non-selective β-adrenergic inhibitors with ISA and local anaesthetic properties) and bupranolol, a substance chemically related to propranolol, although with higher β-inhibiting activity, (Bonomi and Steindler, 1975, Bucci, 1976, Di Tizio et al 1976 and Krieglstein et al 1977)

Atenolol eye drops 1 and 2% i e concentrations lower than that used by Phillips et al (1976, 1977) were also demonstrated to lower the IOP significantly Only a slight dose-dependence was noted, and it could not be verified statistically However, a dose-dependence with topical atenolol may exist for concentrations lower

a transitory rise in IOP after treatment with topical epinephrine, which could be blocked by propranolol, was demonstrated by Kirton and Viernstein (1972) This increment was ascribed to a decreased outflow facility Experiments in monkeys by Törnqvist (1966) and Casey (1966) corroborated the evidence that a ß-receptor mediated relaxation of the ciliary muscle was involved in the reduction of the facility of outflow On the other hand Bill (1970) found that isoproterenol in monkeys increased the facility of outflow but also increased the production of aqueous humor It is difficult to offer an unitary explanation of these findings, whose discrepancy may partly be attributed to species differences

Different ß-blockers have been reported to variously affect the facility of outflow in man An increase of the outflow facility was described for oral proprano ol (Coté and Drance 1968, Takase 1976) and oral bupranolol (Takase and Nanba 1976) A more moderate increase has been reported after topical oxprenolol and bupranolol (Di Tizio et al 1976 Krieglstein et al 1977) No effect on the outflow resistance was primarily observed during application of topical pindolol (Bonomi and Steindler 1975) and topical timolol (Zimmerman et al 1977) However Bonomi and Steindler (1975) noticed a slight effect after one month's administration On the other hand the facility of outflow was found to be significantly decreased by topical propranolol (Tieri and Polzella 1975)

Thus cumulative evidence indicates that ß-blocking drugs variously affect the facility of outflow but these substances have in common a tension lowering effect These results suggest that other mechanisms are involved in the decrease of IOP

The local anaesthetic effect of propranolol was suggested

Bietti (1972) and Bietti et al (1972), who found an additive effect of topical propranolol and pilocarpine The additive effect of combined pilocarpine and atenolol argues against the hypothesis proposed by Phillips et al (1977) that pilocarpine may reduce the effect of atenolol by causing contraction of the ciliary muscle and thereby prevent penetration of topical atenolol into the ciliary processes

Possible mode of action on intraocular pressure

Sympathetic innervation of the ciliary processes and the ciliary body in monkeys and in man has been demonstrated by Ehinger (1966) and Laties and Jacobowitz (1966) But, the iridocorneal angle is only sparsely innervated (Ehinger, 1971) Adrenergic amines have been found to influence processes fundamental in the regulation of the IOP, such as aqueous humor outflow, production of aqueous humor and uveal blood flow (Langham, 1971) Paradoxically both α- and β-adrenergic agonists and antagonists have been described to reduce the IOP (Editorial Br J Ophthalmol 1975 Chiou and Zimmerman, 1975)

Data on the influence of β-receptors in the regulation of intraocular pressure was first presented by Weekers et al (1955) who demonstrated a decrease in IOP during administration of topical isoproterenol, mainly a β-agonist, in patients with open-angle glaucoma These observations were later confirmed by other authors (Ross and Drance, 1970 Langham et al 1971) Further Ross and Drance (1970) described in addition to the dose-dependent decrease in IOP by isoproterenol, a preceding, dose-related increase in IOP in patients with ocular hypertension In rabbits

a transitory rise in IOP after treatment with topical epinephrine, which could be blocked by propranolol, was demonstrated by Norton and Viernstein (1972) This increment was ascribed to a decreased outflow facility Experiments in monkeys by Tornqvist (1966) and Casey (1966) corroborated the evidence that a β-receptor mediated relaxation of the ciliary muscle was involved in the reduction of the facility of outflow On the other hand, Bill (1970) found that isoproterenol in monkeys increased the facility of outflow but also increased the production of aqueous humor It is difficult to offer an unitary explanation of these findings whose discrepancy may partly be attributed to species differences

Different β-blockers have been reported to variously affect the facility of outflow in man An increase of the outflow facility was described for oral propranolol (Coté and Drance 1968 Takase 1976) and oral bupranolol (Takase and Nanba 1976) A more moderate increase has been reported after topical oxprenolol and bupranolol (Di Tizio et al 1976 Krieglstein et al 1977) No effect on the outflow resistance was primarily observed during application of topical pindolol (Bonomi and Steindler 1975) and topical timolol (Zimmerman et al 1977) However Bonomi and Steindler (1975) noticed a slight effect after one month s administration On the other hand the facility of outflow was found to be significantly decreased by topical propranolol (Tieri and Polzella 1975)

Thus cumulative evidence indicates that β-blocking drugs variously affect the facility of outflow, but these substances have in common a tension lowering effect These results suggest that other mechanisms are involved in the decrease of IOP

The local anaesthetic effect of propranolol was suggested

by Musini et al (1971) to be responsible for the IOP reducing effect, observed during administration of this compound But such a mechanism seems unlikely, as also other β-adrenoceptor antagonists, such as practolol and atenolol, lacking this property, have been shown to reduce IOP to the same extent as propranolol Neither did the present investigation (V) produce evidence in support of such a mechanism since application of topical atenolol was followed by a clear fall in tension without variation of the corneal sensitivity

As propranolol influences the smooth muscles of the blood vessels by inhibiting a β_2-mediated vasodilatation, one could expect that the episcleral venous pressure would change during treatment with propranolol and thus contribute to a reduction of outflow resistance However, in the present investigation the episcleral venous pressure remained uninfluenced by propranolol (IV) Neither did oral practolol oral atenolol (IV) or topical atenolol (VI) affect the pressure in the episcleral veins, which speaks against the fall in IOP observed during β-inhibition being dependent on changes in the veins of the episcleral plexus

However, in the present investigation a significantly diminished response following repeated tonometry was demonstrated during administration of substances interfering with adrenergic β_2-receptors (propranolol inhibiting β_2-receptors and terbutaline, stimulating β_2-receptors) According to Krakau and Wilke (1974), repeated applanation tonometry should decrease IOP by influencing the vascular system receiving the aqueous humor The finding suggests that a β_2-adrenergic component may affect the regulation of the vascular system collecting the aqueous humor

One possible explanation would be a decrement in the rate of aqueous humor formation as Bill (1970) found an increased production of aqueous humor in monkeys treated with isoproterenol This effect could be inhibited by propranolol However isoproterenol has no effect on the secretory activity of the ciliary body in the rabbit in vitro (Berggren 1970) Further there are several reports describing a reduced formation of aqueous humor during isoproterenol treatment in both animals and man (Eakins 1963 Ross and Drance 1970 Langham et al 1971 Gaasterland et al 1973)

As most publications concerning tonography and IOP in man present no convincing evidence of increased facility of outflow during β-adrenoceptor blockade a reduced aqueous humor formation seems to be the most plausible explanation of the reduced IOP also by β-inhibition

Effect on blood pressure and heart rate

During systemic administration of propranolol and atenolol an influence of the heart rate and to lesser degree systemic blood pressure was observed in most of the studies (I II III IV) As also observed by Macdonald et al (1976) administration of oral propranolol caused a maximal and significant decrease in heart rate within 2 hours in patients with ocular hypertension (I) A similar time-course was also described by Aellig (1976) for the suppressive effect of propranolol on exercise-induced tachycardia in healthy volunteers The decrement in heart rate (13-17 beats/min) in patients was found to persist throughout the 7 day period of treatment with oral propranolol (II) which

is in agreement with the observations published by LeWinther et al (1975) These authors described a mean reduction of 12 beats/min in resting heart rate in healthy volunteers during treatment with oral propranolol (160 mg/day) for 14 days

Unlike propranolol and atenolol, systemic practolol did not affect the pulse rate in healthy volunteers (IV) This is explained by the fact that drugs with ISA can counterbalance the inhibited β-adrenoceptor in normal subjects (Conolly et al 1976)

In the multiple-dose study a small but significant fall in systolic blood pressure of patients with elevated IOP was demonstrated both in the beginning and at the end of a 7 day period of treatment with oral propranolol (80 mg/day) (II) According to Hansson and Hood (1977), an antihypertensive effect of β-adrenoceptor blocking drugs can be seen within 48 hours, a finding in agreement with our observation A decrement in systolic pressure associated with that in IOP has also been described by Cote and Drance (1968) in patients treated with oral propranolol

In normal subjects oral propranolol decreases the systolic blood pressure significantly (LeWinther et al 1975) In the present investigations (III, IV) a significant fall in systolic pressure was observed in the groups treated with propranolol and atenolol, while practolol failed to reduce systolic pressure significantly in one of the studies (IV) The diastolic blood pressure was only moderately affected

In the present study topically administration of atenolol did not affect circulatory parameters (V) Neither did Katz et al (1976) and Zimmerman and Kaufman (1977 a b) find any influence on circulatory parameters with topical timolol These findings argues against a blood-pressure mediated effect, responsible for

the decrease in IOP

Side-effects

General side-effects of β-adrenergic inhibition such as gastritis diarrhoea asthenia and insomnia are well-known phenomena (Hansson and Hood 1977) and of limited importance More serious is the so-called oculomucocutaneous syndrome i e occurrence of keratoconjunctivitis sicca conjunctival scarring nasal and mucosal ulceration and rashes described during treatment with practolol (Felix et al 1974 Wright 1974 1975) which has restricted the use of the substance In the present study the periods of treatment with practolol were short and no oculomucocutaneous side-effects observed In some of the healthy volunteers mild side-effects similar to those reported by Pandolfi and Ohrstrom (1974) were noted during systemic treatment with the three β-adrenergic blocking drugs tested but not to such an extent as to prevent the completion of the trial

In agreement with Phillips et al (1977) no adverse effects were reported by the patients treated with topical atenolol alone When treated with combined atenolol and pilocarpine two patients complained of itching and ocular discomfort Similar symptoms after instillation of other β-adrenoceptor blocking drugs such as propranolol and oxprenolol have been reported by Vale et al (1972) Gos et al (1975) and Bucci (1976) These side-effects restrict the clinical use of these drugs as eye drops No intolerance to the drugs has been observed with topical pindolol (Bonomi and Steindler 1975) and timolol (Katz et al 19 6 Zimmerman and Kaufman 1977 a, b) Like timolol atenolol

has no local anaesthetic properties and therefore it may be suitable for topical application However, long-term clinical investigations are necessary before atenolol can be recommended for routine clinical use

CONCLUSIONS

Observations made in the present investigation appear to warrant the following conclusions

A single dose of oral propranolol demonstrably reduces the IOP within 1 hour and reaches its maximum effect within 3 hours The effect seems to be dose-related The absolute fall in IOP is slightly greater in patients with initially higher untreated IOP A small dose (80 mg/day) of oral propranolol reduces the IOP in patients with ocular hypertension to about the same extent as pilocarpine (2% three times a day) Combined propranolol and pilocarpine cause a larger decrease in IOP than pilocarpine alone

Oral propranolol (80 mg/day) practolol (200 mg/day) and atenolol (100 mg/day) lower the IOP to roughly the same extent in normal.

The episcleral venous pressure (Prv) in normals is not influenced by systemic administration of propranolol practolol or atenolol Topical atenolol causes no change in the Prv of patients with intraocular hypertension

A diminished IOP response following repeated tonometry of normals is seen during systemic administration of propranolol uch a decrease occurs also after administration of practolol and itenolol but is not statistically significant

Topical atenolol demonstrably lowers IOP in patients with ocular hypertension within 1 hour and reaches its maximum effect within 2-3 hours Atenolol eye drops (2% three times a day) appear to be equally effective as pilocarpine eye drops (2% three times a day) in lowering the IOP Combined atenolol and pilocarpine reduce the IOP more than either substance alone

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